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Volume 316, Issue 5827

COVER

A difference as subtle as holding a pencil between one's lips or teeth can influence one's emotional responses. See the Review by Niedenthal within the special section on behavioral science beginning on page 996 and the related Editorial on page 953. A report on career opportunities for behavioral scientists begins on page 1058.

Photo: Chris Maddaloni

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GENETICS

Genome Sequence of *Aedes aegypti*, a Major Arbovirus Vector
V. Nene et al.
The genome of the mosquito that carries dengue and yellow fever consists of almost 50 percent transposable elements and over 15,000 protein-coding genes.
10.1126/science.1138878

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Saturation of the Southern Ocean CO_2 Sink Due to Recent Climate Change
C. Le Quéré et al.
The amount of CO_2 taken up by the Southern Ocean, a major sink, has decreased since 1981, despite the continued increase in atmospheric CO_2 levels.
10.1126/science.1136188

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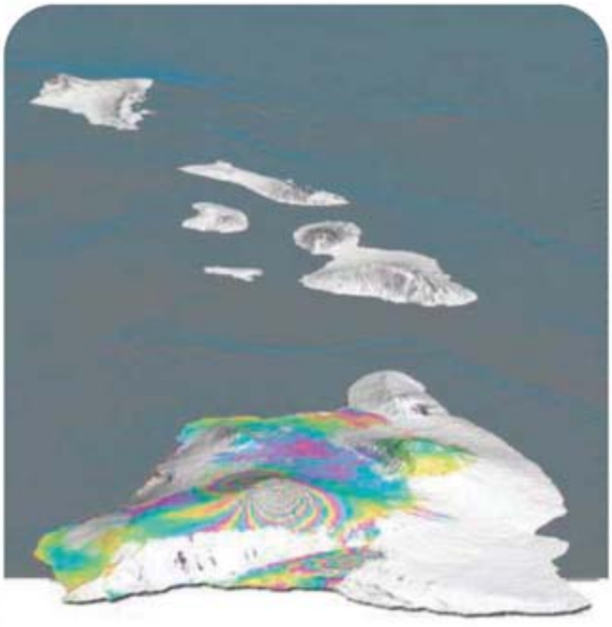
Locating the Two Black Holes in NGC 6240
C. E. Max, G. Canalizo, W. H. de Vries
Adaptive optics are used to pinpoint the positions of two black holes in the collision zone between two merging galaxies.
10.1126/science.1136205

MOLECULAR BIOLOGY

RNA Maps Reveal New RNA Classes and a Possible Function for Pervasive Transcription
P. Kapranov et al.
Analysis of all the RNA transcribed from the human genome reveals three new classes of RNA that may be functionally important.
10.1126/science.1138341

TECHNICAL COMMENT ABSTRACTS

CELL BIOLOGY



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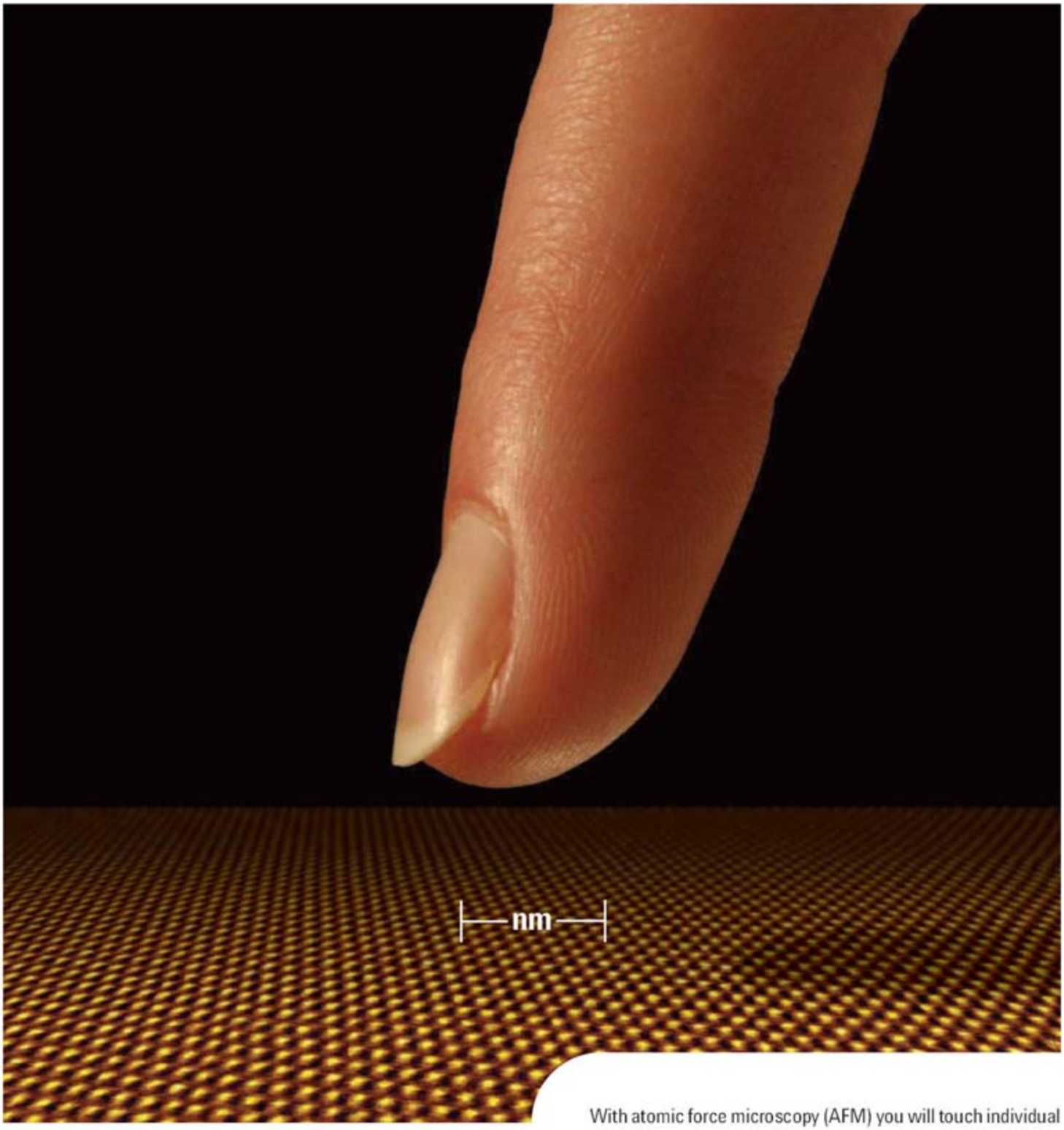

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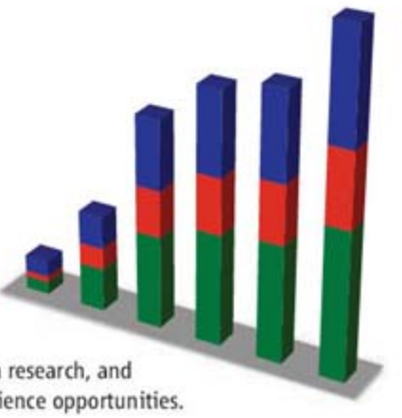

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MicroRNAs induced by pro-inflammatory mediators may provide a link between inflammation and cancer.

PERSPECTIVE: Book Review—Plant Gene Expression
A. Rose
The book "Regulation of Gene Expression in Plants: The Role of Transcript Structure and Processing" is a slim volume providing a useful review of gene expression in plants.

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GLOBAL: Special Feature—Behavioral Science Careers
J. Austin
Behavioral science training provides a solid foundation for a wide range of professional careers.
>> *Careers in Behavioral Science feature p. 1058*

US: Tooling Up—Getting Stuck
D. Jensen
Of all career traps, having a narrow specialty is probably the worst one.

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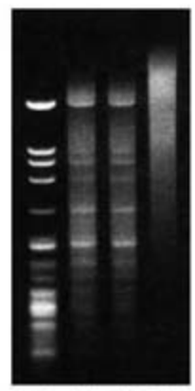

Ligation of blunt-ended HaeIII fragments of Lambda DNA using various amounts of T4 DNA Ligase (400,000 cohesive end units/ml) in a 20 µl reaction volume. Reactions were incubated for 30 minutes at 16°C.

Ligation of HindIII fragments (4-base overhang) of Lambda DNA using 1 cohesive end unit (1µl of 1:400 dilution) of T4 DNA Ligase. Reactions were incubated at 25°C.

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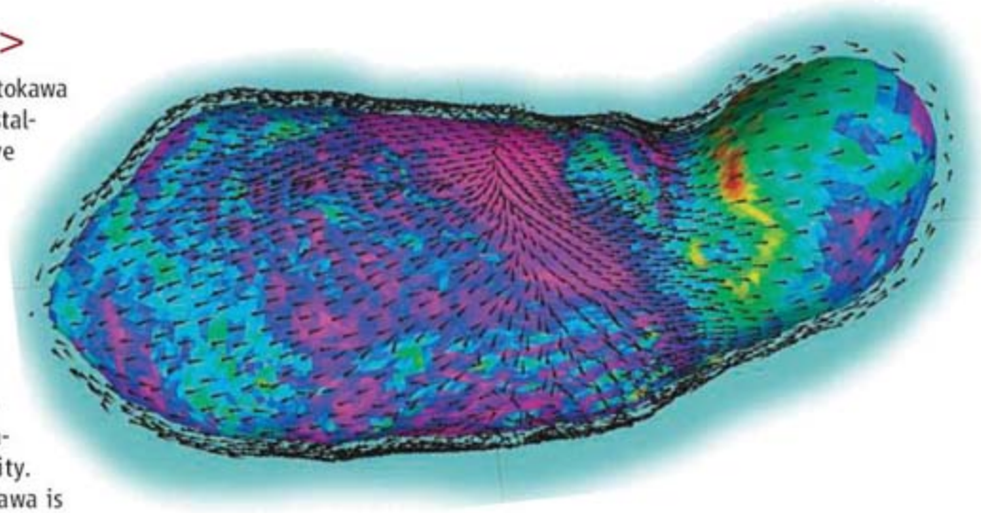
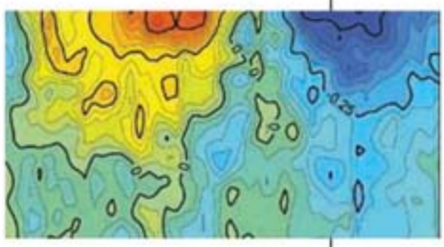


The Hayabusa spacecraft landed on the Itokawa near-Earth asteroid in 2004 and took crystal-clear pictures of the surface that resolve gravels just centimeters in size. **Miyamoto *et al.*** (p. 1011, published online 19 April; see the Perspective by **Asphaug**) analyzed the surface distribution of the boulders and gravels to document granular processes at work such a low-gravity environment. The regolith appears to have been sorted by shaking, such that the finest material congregates in areas of lowest local gravity. Clumping of larger rocks suggests Itokawa is also stirred up from below by convection of grains.

Spinning Up New Production

Mesoscale eddies—transient, rotating patches approximately 100 to 200 kilometers in diameter—occur throughout the ocean and thought to be important causes of mixing in the upper layers. Plankton blooms are regularly observed to occur within these eddies, which suggests that some of these eddies could be the source of nutrients yet unaccounted in biological production in the subtropics. However, because these eddies are so ephemeral, they have been difficult to characterize experimentally, until now (see the Perspective by **Michaels**). **McGuillicuddy *et al.*** (p. 1021) made measurements of chlorophyll, diatom abundance, and oxygen in 10 mode-water eddies in the Sargasso Sea, and used a model that includes an asymmetric response of eddies to surface winds to explain the upwelling and associated plankton blooms that they observed. **Benitez-Nelson *et al.*** (p. 1017) took advantage of the characteristic wind patterns around the Hawaiian Islands to make direct biological, chemical, and physical time-series measurements of a large bloom in a recurrent mesoscale eddy there. The bloom was highly productive, but most of the biologically fixed carbon was recycled in the upper water column and not exported to depth, contradicting the assumption that eddies remove carbon from the cycle and promote enhanced sequestration. Their observations do suggest, however, that eddies are a mechanism for preferential removal of silica from upper waters.



CREDITS (TOP TO BOTTOM): THE UNIVERSITY MUSEUM, UNIVERSITY OF TOKYO/JAXA; BENITEZ-NELSON ET AL.

Polariton Condensation

When bosons are packed together such that the density exceeds a critical threshold, and when temperatures sufficiently low, they can undergo a phase transition and condense into a single quantum state. This Bose-Einstein condensation has been demonstrated in a number of systems, including cold atoms, superfluids, and superconductors, there is a desire, because of the small effective mass (and the potential to drive the phenomenon to higher temperatures) to create condensed states in semiconductor systems. **Balili *et al.*** (p. 1007; see the Perspective by **Littlewood**) show that an ensemble of polaritons, which are quasiparticles formed by photons coupled to excitons, can be generated and trapped in a microcavity in a way analogous to cold-atom traps. The authors then demonstrate the signatures of Bose-Einstein condensation in their system.

Buckle Up

A combination of shallow dike intrusions and earthquakes causes the surface of active Mauna Loa volcano on Hawaii to flex, but it has not been known how the magma beneath the volcano pools and circulates. **Amelung *et al.*** (p. 1026) have mapped the topography of Mauna Loa from 2002 to 2005 using interferometric synthetic aperture radar observations. A new dike-like magma body is swelling in the belly of the volcano in the southwest rift zone. The magma accumulation occurs in a region that was unclamped by previous activity, dike intrusions and earthquakes, which suggests that local stress transfer plays an important role in subsurface magma build up.

Mental Block

Young children realize that unsupported objects fall to the ground long before they are taught about gravitational attraction. Intuitions such as these can then hamper the learning of scientific facts, such that the world is round, and not flat. **Bloom and Weisberg** (p. 996) review the notion that beliefs that become established early in life, especially about topics where detailed understanding is practically impossible to achieve directly, contribute to an adult proclivity that renders much of modern science counter-intuitive and hence less readily accepted.

Morality and Emotion

Although morality is partly a game of self-promotion, people usually do sincerely want peace, decency, and cooperation to prevail within the groups they operate. **Haidt** (p. 998) reviews how these motives are implemented in large part by a variety of emotionally governed intuitions that arise quickly and automatically, and which then guide controlled processes such as moral reasoning. Much of the information that we are exposed to is perceived and processed without our being fully aware of it, and this situation may be particularly true for emotions. **Niedenthal** (p. 1002) reviews the

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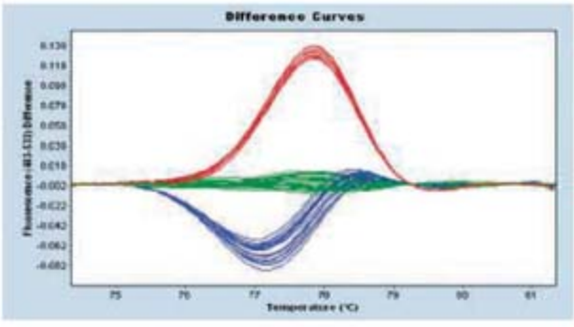

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Continued from page 949

connection between perceived, retrieved, and even experimentally induced emotions and how we process emotional information.

From Leaf to Flower

As spring begins, many plants turn to flower under the control of florigen. The molecular nature of florigen has long been unknown, but the signal was known to originate in leaves, and thus had to travel through the plant to the growing buds. Now **Corbesier *et al.*** (p. 1030, published online 19 April) and **Tamaki *et al.*** (p. 1033, published online 19 April) show that it is a protein rather than its coding RNA that is the likely florigen signal that moves within the plant (see the 20 April news story by **Pennisi**). The florigen RNA and protein are encoded by the *FLOWERING LOCUS T* gene in *Arabidopsis* and the *Hd3a* gene in rice.

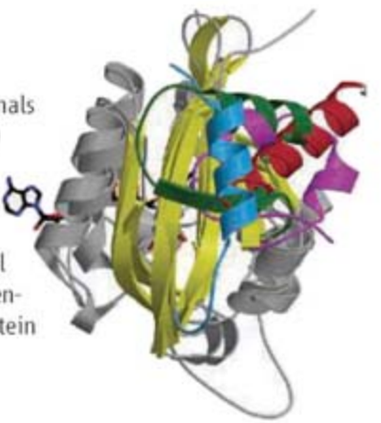
Smart Drugs, Smarter Tumors

A promising class of "smart" cancer drugs work by inhibiting specific tyrosine kinases linked to uncontrolled growth. Gefitinib and erlotinib, drugs that target the kinase activity of the epidermal growth factor receptor (EGFR), can be very effective when initially administered to lung cancer patients whose tumors contain activating mutations in the *EGFR* gene. Almost inevitably, however, these tumors develop resistance to the drugs and begin to regrow. **Engelman *et al.*** (p. 1039, published online 26 April) find that drug resistance in a subset of these tumors is caused by amplification of the *MET* oncogene, an event that in turn activates, via a different route, the same cellular signaling pathway originally activated by the mutant EGFR.

Tumor Suppressor Joined to WNT Network

Elucidation of the cellular signaling pathways that contribute to cancer development often begins with the identification of a gene mutated in human tumors. Complementary biochemical approaches become especially important when the sequence of the newly identified gene provides few clues as to its function. **Major *et al.*** (p. 1043; see the Perspective by **Nusse**) used analysis of protein interaction networks to define the function of *WTX*, a tumor suppressor gene found very recently to be mutated in an inherited kidney cancer called Wilms tumor. The WTX protein forms a complex with several proteins in the WNT signaling cascade, including β-catenin, AXIN1, β-TrCP2 (β-transducin repeat–containing protein 2), and APC (adenomatous polyposis coli) and antagonizes WNT signaling by promoting β-catenin degradation.

Seeing the Light



For organisms to adapt to environmental changes, external signals must affect protein function. Proteins in the PAS (Per-Arnt-Sim) superfamily are involved in transducing diverse external signals, but it has been a challenge to define the signaling pathways. **Zoltowski *et al.*** (p. 1054) have determined crystal structures for the dark- and light-activated states of a fungal photoreceptor. Light-induced chemical changes at the active center propagate to large-scale conformational changes at the protein N-terminus that are essential for cellular function.

Making Centrioles

Centrioles play a key role in the organization of the microtubule cytoskeleton in animal cells, particularly during mitosis when they are responsible for generating the mitotic spindle poles. **Rodrigues-Martins *et al.*** (p. 1046, published online 26 April) now show that overexpression of the SAK/PLK4 kinase in the *Drosophila* germ line drives a dramatic amplification of centrioles in syncytial embryos producing thousands of centrioles. Centrioles are eliminated from eggs during oogenesis, and so the centriole is normally provided by the sperm upon fertilization. However, centriole amplification was observed in unfertilized eggs that are devoid of centrioles, indicating that centrioles can be generated de novo. Thus, centriole formation may represent a self-assembly process in which a preexisting centriole can act as a catalyst and platform for centriole assembly, and in which feedback mechanisms regulate centriole number.

CREDIT: ZOLTOWSKI *ET AL.*

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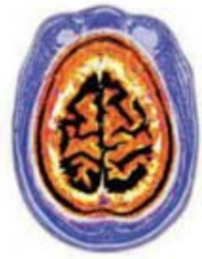
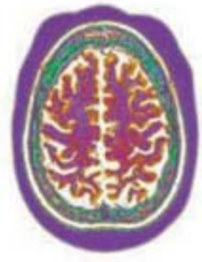
Behavioral Science Comes of Age

PEOPLE ARE FASCINATED BY THE BRAIN, IN LARGE PART BECAUSE OF A GREAT INTEREST IN understanding their own minds and mental health. Over a century of neuroscience and psychological research has convinced most people that "Descartes died," leaving the old mind/brain dualism behind. The reality that we don't have a mind separate from the rest of our body has been brought home in many experimental ways, perhaps especially by modern neuroimaging techniques that allow investigators to look into the brains of living, awake, and behaving human beings—watching minds in action.



That the brain is the seat of the mind does not necessarily mean that a purely reductionist approach will, in the long run, fully explain the workings of the mind. In fact, there is no evidence that we will be able to understand all aspects of the mind simply in molecular neurobiological terms. At the same time, a purely "up-uctionist" approach won't meet the need either. We can't understand the mind through working only at the behavioral level. Instead, we will need both biological and behavioral research, separately and in combination.

Great progress has been made in the past decade in neuroscience, behavioral science, and behavioral neuroscience, and we now have the scientific sophistication to make even more rapid advances in understanding the brain and mind. Neuroscience is among the fastest-growing disciplines of biology and has shown extraordinary recent productivity. Indeed, we have probably learned more about the brain in the past 20 years than in all of recorded history.



Over the same period, behavioral science has also come of age, having moved way beyond simple studies of rats running in mazes and simple theories of human behavior that caused many scientists to doubt the power of analysis at that level. As a psychologist trained in the 1960s, I frequently had to fend off allegations that psychological science served primarily to confirm common sense; but behavioral science now more often revises conventional wisdom. For example, as recently as 35 years ago, newborn infants were believed to be incapable of learning about their worlds. But subsequent decades of research on infants have falsified that belief by showing how newborns acquire information about and interact with their environments.

Three Reviews in this week's *Science* illustrate how behavioral science is making progress in explaining such complex concepts as how people process emotionally significant information (Niedenthal, p. 1002), how morality can be both universal and culturally variable (Haidt, p. 998), and how children develop resistance to scientific explanations if those explanations contradict their common-sense views of the world (Bloom and Weisberg, p. 996).

When *Science* posted its list of the 125 most challenging and important questions facing the scientific enterprise in July 2005, many were behavioral in nature or had components requiring a collaborative approach that included behavioral scientists: "What is the biological basis of consciousness?" "How are memories stored and retrieved?" "How did cooperative behavior evolve?" "Why do we dream?" "How much of personality is genetic?" Behavioral scientists, often working in multidisciplinary teams, are making progress on each of these.

Sophisticated behavioral analyses are also being applied to many of the most pressing societal issues of our era. Understanding terrorism is among the most timely and challenging; equally important is exploring the mechanisms through which poverty exerts its pervasive effects and how we might mitigate or prevent them. Advances in behavioral science are also expanding the effectiveness of our strategies for promoting public health. And research on cognitive styles and other aspects of how people learn holds great promise for promoting the success of educational systems throughout the world.

Unfortunately, the evolution of behavioral science and its contributions in many domains have not received the public recognition they deserve. One consequence is that policymakers still give short shrift in budget allocations to behavioral science research. Now that it has proven its quality and its contributions to the major issues of the day, behavioral science deserves the same respect and support given to any scientific field that has come of age.

– Alan I. Leshner

10.1126/science.1144897

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There are few awards more rewarding in science than the *Science*/AAAS and GE Healthcare-sponsored prize – just ask the Grand Prize winner for 2006. In addition to having her essay published in *Science*, Irene Chen received $25,000, was flown to the awards ceremony in Stockholm, Sweden, and got to pick the brains of Nobel laureates Andrew Fire and Craig Mello**.

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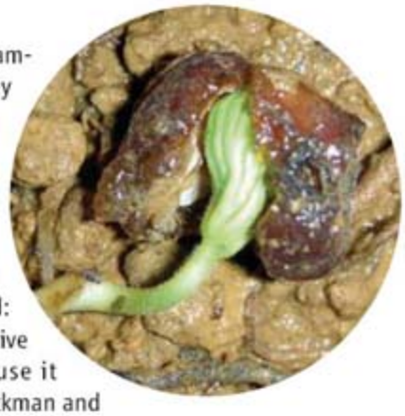
* For the purpose of this prize, molecular biology is defined as "that part of biology which attempts to interpret biological events in terms of the physico-chemical properties of molecules in a cell" (McGraw-Hill Dictionary of Scientific and Technical Terms, 4th Edition).

**Nobel Prize winners in Medicine for their discovery of RNA interference – gene silencing by double-stranded RNA.

Collecting *Oenocarpus mapora* seeds (above); germinating *Cordia* seed (right).

ECOLOGY/EVOLUTION

Hunting in Forests



The killing of large vertebrates by humans can have ramifications beyond the immediate effects on the prey populations themselves. There is growing evidence that harvesting of animals from tropical forests affects the entire ecological community. In particular, the dispersal of plant seeds is altered when their animal sowers are depleted by hunting; this in turn has long-term consequences for tree species composition in the forest. The outcomes may be unexpected: in some cases, hunting can actually increase the relative abundance of large-seeded plant species because it reduces seed predation pressure, as described by Beckman and Muller-Landau. The hunting of vertebrates can also affect invertebrate populations. For example, a reduction in the amount of dung directly stresses the populations of dung beetles. These and other sequelae of hunting in tropical forests, and the steps that might be taken to reduce hunting pressure, are discussed in 10 papers in a special section edited by Wright and Stoner. — AMS

Biotropica **39**, 328; 289 (2007).

VIROLOGY

Probing Neurodegeneration

Although great strides have been made toward the global eradication of poliovirus, this pathogen continues to be studied intensely in research labs, in part because history has shown that identification of the cellular pathways disrupted by viruses can provide fundamentally important insights into disease. One mystery yet to be solved is how poliovirus causes the motor neuron degeneration that leads to the muscle weakness and paralysis typical of poliomyelitis.

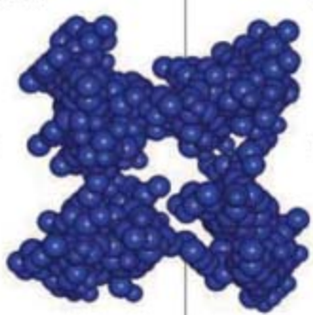
A tantalizing clue has emerged from the work of Almstead and Sarnow, who have identified a potentially unifying molecular feature of poliomyelitis and spinal muscular atrophy, an inherited neurodegenerative disease. Spinal muscular atrophy arises from loss or mutational inactivation of the gene encoding the survival of motor neurons (SMN) protein. Together with eight other proteins called Gemins, SMN is part of a dynamic macromolecular complex that facilitates the assembly of ribonucleoprotein complexes implicated in pre-mRNA splicing. The splicing complexes are built around a so-called Sm core of RNA-binding proteins, and patients with spinal muscular atrophy show reduced levels of Sm core assembly. The authors show that poliovirus infection inhibits Sm core assembly through viral-mediated proteolysis of Gemin3, a critical component of the SMN complex. The downstream effects of reduced Sm core formation on motor neuron survival have been contentious, but poliovirus may serve as a useful research tool for exploring this issue. — PAK

Genes Dev. **21**, 1086 (2007).

CHEMISTRY

Aligned for Speed

In purple photosynthetic bacteria, a ring of bacteriochlorophyll molecules assembles through noncovalent interactions to form the light-harvesting antenna complex. The ultrafast energy transfer rates of such complexes can be approached in mimic complexes with covalently linked chromophores, but complexes more efficiently synthesized through self-assembly have exhibited slower rates because of nonoptimal alignment of the molecular dipoles. Kelley *et al.* prepared a zinc chlorophyll derivative and established through small-angle x-ray scattering (SAXS) that it self-assembles into tetramers (shown above) in toluene solution. Transient absorption spectra reveal a much faster Förster energy transfer rate in this complex than in prior porphyrin tetramers; however, the rate was still 10 times slower than in the fastest photosynthetic proteins, suggesting that the dipole alignment could be optimized further. — PDS



J. Am. Chem. Soc. **129**, 10.1021/ja071362a (2007).

APPLIED PHYSICS

To Know a Tortured Flow

When stresses induce flow of non-Newtonian fluids, such as paint or whipped cream, the fluid viscosity may depend on the shear strain rate and/or the length of time that the stress is applied. Common industrial processes in which polymer or surfactant solutions move through porous media also involve non-Newtonian flows. In these cases, the fluid properties depend on the local velocity gradients and hence the local pore structure; modeling based on macroscopic approximations tends to fail.

Sullivan *et al.* have developed a hydrodynamic lattice Boltzmann (LB) method for quantitative three-dimensional simulations of non-Newtonian flow through disordered porous media. The key to their method is the use of ^{1}H magnetic resonance imaging to accurately model the porous media. The authors examined four fluids: two Newtonian and two that showed a reduction in viscosity with increasing strain rate. For the flow profile across a transverse two-dimensional slice, the difference between the experimental and simulated flow values was small (~4% of the average velocity). In comparisons between two fluids with similar overall flow rates, the more shear-thinning fluid showed increased dispersion, with more high-velocity

Continued on page 957

CREDITS (TOP TO BOTTOM): NOELLE BECKMAN; KELLEY *ET AL.*, *J. AM. CHEM. SOC.* **129**, 10.1021/JA071362A (2007)

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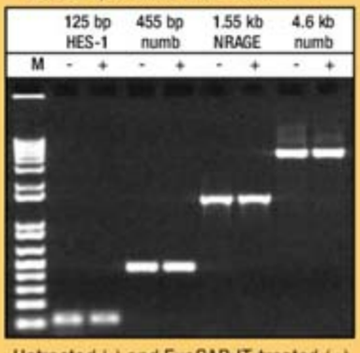

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Fueling Innovation in Life Science

Continued from page 955

channels as well as more stagnant ones, consistent with macroscopic observations. — MSL

J. Non-Newtonian Fluid Mech. **143**, 59 (2007).

CLIMATE SCIENCE

Melting Faster

Observations of the extent of Arctic sea ice in September—at the end of the melt season, when ice coverage is at its annual minimum—have shown a large decline over the past several decades, consistent with current qualitative understanding of natural variability and the effects of a warming climate. Nearly all climate models predict that September Arctic sea ice extent will continue to decline through the 21st century, largely in

response to rising concentrations of atmospheric greenhouse gases. How well do observations and models agree, though? To answer that question, Stroeve *et al.* compared the output of the more than a dozen models participating in the Intergovernmental Panel on Climate Change Fourth Assessment Report that calculated sea ice. They found that nearly all of the models overestimated annual minimum Arctic sea ice area, in many cases by large amounts. These findings have two important implications: first, that the effect of rising greenhouse gases may have been more important than has been believed; and second, that future loss of Arctic sea ice may be more rapid and extensive than predicted. — HJS

Geophys. Res. Lett. **34**, L09501 (2007).

VIROLOGY

Shifting Landscapes

Influenza epidemics are thought to emerge as a result of escape from host immunity as the viral genome mutates along a trajectory of antigenic drift. However, a puzzle for influenza epidemiologists is the limited diversity of observed antigenic types. Recker *et al.* present a model in which successive antigenic types emerge independently of the mode or tempo of mutation in a cyclical manner. The model is consistent with data from hemagglutination inhibition assays of H3N2. The authors suggest that rather than virus mutation driving the epidemiology of influenza, the changing landscape of host population immunity governs whether and when epidemics emerge. Much of the epidemiology of influenza, such as the re-emergence of an antigenic type, is probably missed in routine clinical data based on detection of symptoms. For instance, data from poultry workers chronically exposed to avian influenza suggest that they enjoy a significant degree of cross-protection against the lethal effects of H5N1. This shift in perspective could have important implications for the way we monitor influenza virus for epidemic prediction and vaccine design. — CA

Proc. Natl. Acad. Sci. U.S.A. **104**, 7711 (2007).

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<< Who You Are Versus Where You Are

The ability to identify essential components by network analysis may provide one means of ranking targets for disrupting specific cellular processes. Yu *et al.* have assessed the relative importance of being a hub (that is, being a highly connected node) in comparison to being a bottleneck, a node that serves as a conduit for nonredundant paths through the network. These attributes do overlap, but they were able to find all four types of nodes in large-scale protein-protein interaction maps: hub-bottleneck, nonhub-bottleneck, hub-nonbottleneck, and nonhub-nonbottleneck. For instance, in signaling networks, hub-bottlenecks and nonhub-bottlenecks were likely to be encoded by essential genes, whereas hub-nonbottlenecks were not. Thus, being a bottleneck may be a better indicator of necessity than the degree of connectedness. A refinement of the nonhub-bottleneck nodes was achieved by dividing them into those that participate in permanent interactions, such as those that hold multisubunit complexes together, versus those that mediate transient protein-protein interactions. Not surprisingly, permanent nodes were more likely to be encoded by an essential gene than were the transients. Furthermore, the authors suggest that nonhub-bottlenecks are key to pathway crosstalk. Cak1p, which is encoded by an essential gene in yeast and is a cyclin-dependent protein kinase–activating kinase, is offered as an example of a nonhub-bottleneck that is the critical link between two signaling pathways: regulation of the cell cycle and sporulation. — NRG

PLoS Comp. Biol. **3**, e59 (2007).

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Information for Authors

See pages 120 and 121 of the 5 January 2007 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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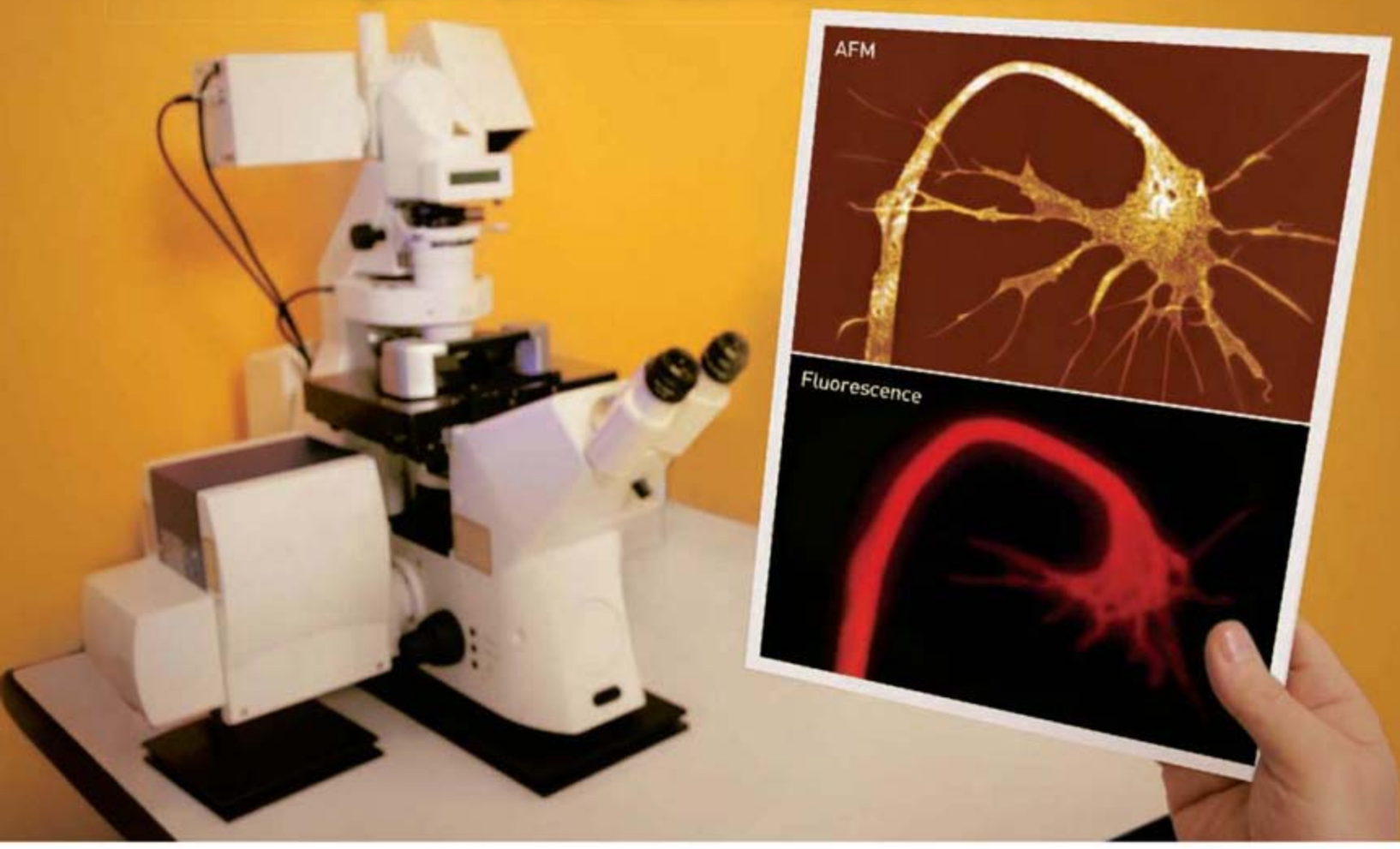

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This Second Life avatar looks healthy—so far.

Playing With Epidemics

Do you have an alter ego in Second Life, the booming virtual world? Watch out: Your double may catch a nasty virus someday. Scientists say introducing infectious diseases into online games could help them study epidemics.

The idea comes from Ran Balicer of Ben-Gurion University of the Negev in Be'er Sheva, Israel, who was inspired by a plague that swept through the online fantasy game World of Warcraft in 2005. To spice things up, game administrators introduced an infectious disease called "corrupted blood." It spread much faster than anticipated, in part because administrators had made virtual "pets" act as reservoirs.

In the future, epidemiologists could work with the administrators of other games to release infectious agents—carefully choosing factors such as mode of transmission, symptoms, and possible treatments—to investigate how diseases spread and how they can be controlled, Balicer wrote in the March issue of *Epidemiology*. Second Life, in which millions of people chat, work, trade, play, and socialize, would be a great testing ground, he says, because it's much more like the real world than is World of Warcraft.

Harvard University disease modeler John Brownstein says the research committee of the International Society for Disease Surveillance held a long discussion about the paper recently and wants to explore the idea. Epidemics in online games would involve decision-making by thousands or millions of real people, Brownstein says, which "adds a level of authenticity that doesn't exist in other simulations."

A Journal Is Created

The intelligent design (ID) movement has suffered setbacks lately, but the biblical literalists known as young-Earth creationists are going strong. This month, the Institute for Creation Research, based near San Diego, California, launched the *International Journal for Creation Research*.

Described as a "professional peer-reviewed journal," the publication promises to supply "hard data based on cutting-edge research" to support theories such as "the young earth model, the global Flood, [and] the non-evolutionary origin of the species."

The editor-in-chief is Andrew A. Snelling, a former geologist for a uranium-mining company who has a Ph.D. from Sydney University and is now in Brisbane, Australia. According to the instructions to authors, papers will be evaluated as to whether they "are formulated within a young earth, young universe framework" and whether they "provide evidence of faithfulness to the grammatico-historical/normative interpretation of Scripture." Snelling could not be reached for comment.

Attempts to demonstrate a scientific basis for ID, the highbrow version of creationism, have failed in court when defenders of evolution have challenged the presentation of ID in science classes. But, notes biologist Kenneth Miller of Brown University, the picture is different at the grassroots level. "Young-Earthers have always represented the bulk" of anti-evolutionists, he says.

NET WATCH

Surfing the Night Sky

Whether you're hunting for data on the M90 galaxy or just feel like a little lunchtime stargazing, drop by WikiSky. You can zoom in on more than 500,000 objects outside our solar system, including stars in the roiling Gamma Cygni nebula (right). Visitors can browse a whole-sky map, customize the view to show the stars above their location, or switch to photos from the Sloan Digital Sky Survey, which is charting one-fourth of visible space. Click on an object to summon data such as its position, magnitude, motion, and distance from Earth. The accounts also furnish photos and links to abstracts of papers that mention the object. Users of the site, created by a pair of mathematicians in Canada, can contribute by writing Wikipedia-style articles on astronomy topics or posting their own heavenly shots. >>

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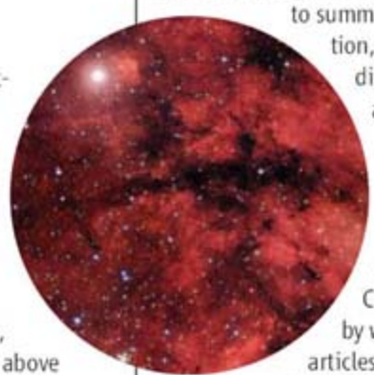

Glimpse of Inner Earth

This surreal landscape shows what scientists say is the deepest hydrothermal vent ever found—4100 meters below sea level on the Mid-Atlantic Ridge. It's from Serpentine, a French-Russian mission that focused on the rare places where magma from Earth's mantle comes in contact with ocean water. Mission leader Yves Fouquet of the French Research Institute for Exploitation of the Sea says the team is particularly interested in the geochemistry and geology of such spots. Biologists aboard the research vessel, *Pourquoi pas?*, also collected samples of new life forms around these hot spots.

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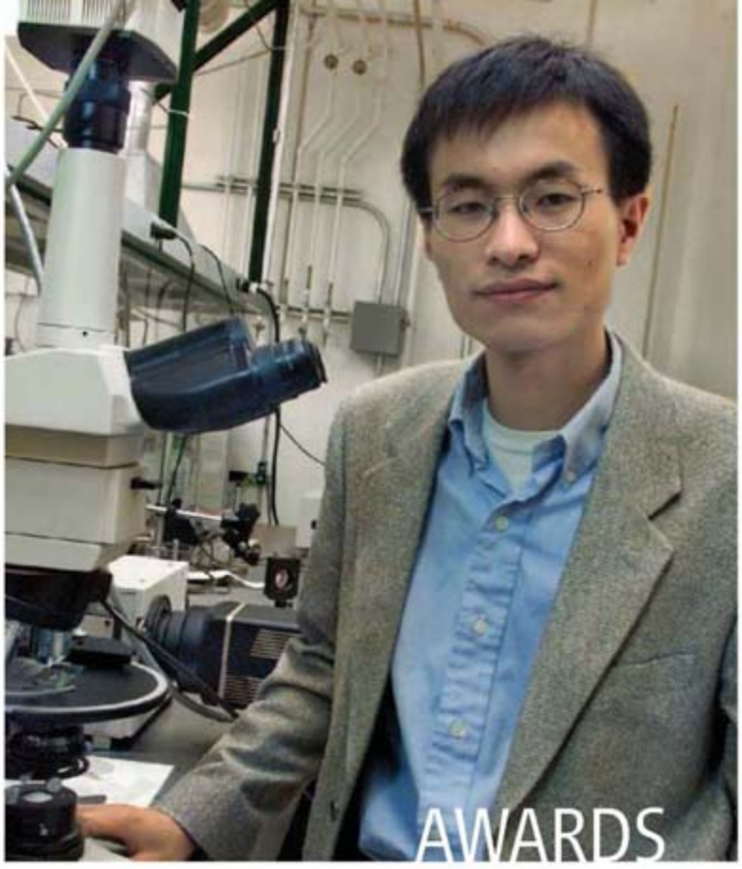

AWARDS

RAPID RISE. Some of the tiniest wires ever made continue to earn great rewards for Peidong Yang, a nanomaterials researcher at the University of California, Berkeley. Last week, the U.S. National Science Foundation gave Yang its $500,000 Waterman Award, a research grant the agency hands out annually to an outstanding young NSF-supported researcher.

The award caps a remarkable run for the 36-year-old Yang, who synthesizes nanowires to make everything from tiny light-emitting diodes and lasers to transistors and solar cells. Yang ranked among the top 10 materials scientists in the world in overall citations from 1995 to 2005, according to the Institute for Scientific Information, even though he didn't earn his Ph.D. until 1997, and his average of more than 100 citations per paper is nearly double that of the next most cited researcher.

Future Waterman winners may soon have company. Last week, the U.S. House of Representatives authorized NSF to give out as many as three such awards each year. "The competition is so fierce that the committee would appreciate the ability to make more than one award," an agency spokesperson told *Science*.

IN BRIEF

French-born astrophysicist **France Córdova** has been named president of Purdue University in West Lafayette, Indiana. Currently chancellor at the University of California, Riverside, Córdova is a former chief scientist at NASA who has also written award-winning fiction and a cookbook. She succeeds Martin Jischke, who is retiring in June.

Chemist **Goverdhan Mehta** of the Indian Institute of Science in Bangalore and biologist **Luis Herrera-Estrella** of Mexico's National Laboratory of Genomics for Biodiversity in Irapuato have won the Trieste Science Prize from the Academy of Sciences for the Developing World. Mehta's contributions to organic synthesis have led to new hybrid cancer drugs. Herrera-Estrella's work on genetically modified crops has been a boon to Latin America. The two will share $100,000.

INSIDE GOVERNMENT

GOING PRIVATE. Alzheimer's disease researcher Trey Sunderland has retired from the U.S. government, closing the book on the most serious case to emerge from the 3-year scandal over financial conflicts of interest at the National Institutes of Health (NIH).

Sunderland, once chief of the geriatric psychiatry branch at the National Institute of Mental Health in Bethesda, Maryland, failed to report more than $600,000 in consulting fees from Pfizer while providing spinal fluid samples to the company for Alzheimer's studies. Last December, he was convicted of violating federal conflict-of-interest laws and sentenced to 2 years of probation, 400 hours of community service, and an obligation to repay $300,000 of his earnings.

Lawmakers criticized NIH and Department of Health and Human Services officials for not firing Sunderland; the officials responded that only the Public Health Service Commissioned Corps could discharge him. That has now happened, NIH said last week. According to a recent report that Sunderland's probation officer filed with U.S. District Court in Baltimore, he retired on 1 April and is now in private psychiatry practice. The report also says he has repaid more than $100,000 of the $300,000 and has completed more than 300 hours of community service.

Movers >>

TO A NEW CONTINENT. U.S.-born stem cell researcher Nadia Rosenthal was charmed by Australia when she went there on a field trip 5 years ago to collect newts. Now, the 54-year-old head of the mouse biology program at the European Molecular Biology Laboratory's (EMBL's) outstation in Monterotondo, Italy, is returning to direct the new $126 million Australian Regenerative Medicine Institute at Melbourne's Monash University (MU).

Rosenthal says she was attracted by MU's two stem cell centers and a research-friendly regulatory environment. Last month, Monash's home state of Victoria ratified a federal law that permits somatic cell nuclear transfer under a license. Besides working on stem cell culture and mouse models, Rosenthal hopes the institute will use the university's new synchrotron to do high-throughput protein crystallography and aid Australia's bid to become an associate member of EMBL. "If you want to plug into European science, this is an excellent pipeline," she says.

Rosenthal's husband, biochemist Alan Sawyer, is also moving from Monterotondo to Monash to establish the $9 million Monoclonal Antibody Technologies Facility.

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No Neandertal interbreeding 967

Last rites for ecology lab 969

RESEARCH INTEGRITY

Sonofusion Back on the Firing Line As Misconduct Probe Reopens

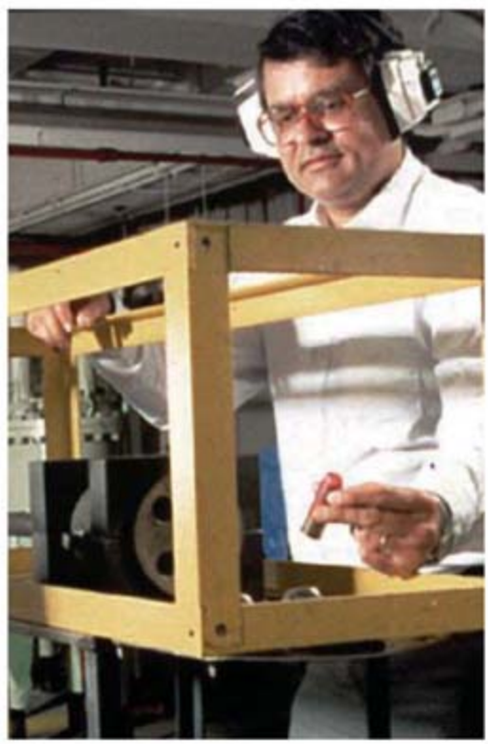
Officials at Purdue University in West Lafayette, Indiana, have launched a new inquiry into bubble fusion researcher Rusi Taleyarkhan, just months after exonerating him of research misconduct. The inquiry was brought to light by a congressional report made public last week, which concluded that in its previous inquiry, "Purdue deviated from its own procedures in investigating this case and did not conduct a thorough investigation."

Taleyarkhan, a nuclear engineering professor at Purdue, pioneered the controversial notion that sound waves can collapse bubbles in a manner that causes atoms to fuse, releasing energy in the process. If true, "sonofusion" holds the prospect of clean and abundant energy. Fusion experts challenged Taleyarkhan's claims from the start. But last year, fellow Purdue researchers turned up the heat when they complained that Taleyarkhan was obstructing their efforts to duplicate the research (*Science*, 17 March 2006, p. 1532).

In response, Purdue officials announced an initial review in February 2006. The university followed it over the summer with a formal inquiry to see whether a full-scale investigation was warranted. This February, Purdue officials announced that their internal investigations had absolved Taleyarkhan of wrongdoing (*Science*, 16 February, p. 921). Critics from both inside and outside the university complained that the inquiry had been too narrowly focused and that the Purdue committee never contacted them so that they could express their concerns. In March, Representative Brad Miller (D–NC), who heads the Investigations and Oversight Subcommittee of the House Committee on Science and Technology, wrote to Purdue President Martin Jischke asking for copies of the university's internal reports.

Although Purdue officials never made public the reports of their proceedings—or even the charges they were investigating—the congressional report quotes from them and makes it clear that the initial inquiry focused on the concern that Taleyarkhan improperly omitted his name as an author from two papers in an effort to make the work look like an independent verification of his research. The House committee argues that even Purdue's narrow investigation found "serious deviations" from commonly accepted scientific practices. Among them: that Taleyarkhan played a significant role in writing the disputed papers and that he placed junior scientists in "precarious positions" in order to promote his research program. "Based on these conclusions, it is difficult to understand how the Inquiry Committee could have then decided that Dr. Taleyarkhan's actions did not constitute research misconduct," the report states.

In an e-mail message to *Science*, Taleyarkhan says he is "appalled" by the congressional report. "As written, the memo/letter presents only the accuser's point of view and passes its verdict on the accusations," he writes. Later, in a phone interview, Taleyarkhan insisted that he had nothing to do with the papers in question and that it's the science of sonofusion that is being lost in the conflict. "Sonofusion is for real. It has been reproduced by groups without a conflict of interest. But it is not yet reproducible on demand," Taleyarkhan says.



Embattled. Taleyarkhan (shown working on an earlier, unrelated experiment) says "sonofusion is for real" and suspicions about his work are groundless.

CREDIT: CURTIS BOLES/OAK RIDGE NATIONAL LABORATORY/AP PHOTO

Joseph Bennett, Purdue's vice president for university relations, says that "Purdue's position is that it did follow its policies correctly" and continues to do so. Shortly after completing the last inquiry, Bennett says the administration received additional allegations regarding sonofusion and has opened a new inquiry, which is expected to take 3 months to complete. Unlike the previous inquiry, the new panel is expected to broaden its scope to probe the integrity of the underlying studies.

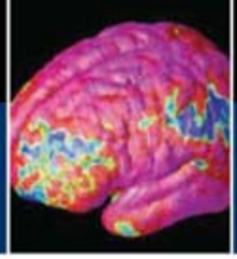
Miller's subcommittee became aware of the new inquiry while reviewing the case. Its report chides Purdue officials for the makeup of the new inquiry panel. According to the report, all three of the panel members served on previous sonofusion inquiry panels, as did the staff member assigned to it. The report recommends adding one or more outside members to ensure the panel's independence, which Jischke says he will do.

Other Purdue faculty members say they will insist on such transparency to protect the university's reputation. "I am somewhat disappointed that the original sets of committees did not do a complete, thorough evaluation of the evidence at the time," says Bernie Tao, a Purdue agricultural engineer who chairs the university senate. The senate was expected to meet this week to draw up a list of recommendations.

Other faculty members say they are concerned about the impact of the conflict on Taleyarkhan's department. Chan Choi, a Purdue nuclear engineering professor, notes that in September, Lefteri Tsoukalas, a critic of Taleyarkhan, stepped down as chair of the nuclear engineering department. Eight months later, he says, the administration has yet to form a search committee to fill the post, despite written pleas from the faculty. Choi adds that the yearlong ordeal has prompted a few students to leave the department, although he says it has not hurt recruitment of new faculty and students. Now with the new inquiry, "we have a golden opportunity to clear our name," Choi says.

–ROBERT F. SERVICE

The mystery of the disappearing bees
970



Nipping psychosis in the bud
976

Smooth transition? Tony Blair (*left*) with his likely successor, Chancellor Gordon Brown.

CREDIT: STEFAN ROUSSEAU/REUTERS

U.K. RESEARCH

Blair Departs After a Decade of Strong Support for Science

As Tony Blair last week announced his intention to step down in June after 10 years as the United Kingdom's prime minister, the British media cited his devastatingly low poll ratings as proof that the Iraq war would overshadow any other legacy for the Labour Party leader. But the U. K.'s scientific community has far warmer feelings toward Blair's government, thanks to its steady and significant increases in funding, its liberal attitude to human embryonic stem cell research, the recruitment of scientists to help shape government policy, and a clampdown against animal-rights extremists. And Blair early on embraced the dangers of climate change as a personal crusade, even making it a focal point of the 2005 summit of the G8 leaders.

When Blair spoke out about science, his enthusiasm was evident. "This government is unabashedly pro-research," says neurobiologist Colin Blakemore, head of the U.K. Medical Research Council. "There is a deep commitment to science and what it can achieve for government."

In 1997, Blair's Administration took over a scientific enterprise that had been slowly starved of funding over 18 years of Conservative government. The first sign of revival came in 1998 in the new government's initial spending review: Research got a 15% boost over 3 years. "[Blair's] interest and commitment to science go right to the beginning," says University of Oxford ecologist Robert May, chief scientific adviser to the U.K. at the time. Over Blair's tenure, the science budget, which supports the grant-giving research councils as well as subscriptions to the likes of the CERN particle physics lab and the European Southern Observatory, has more than doubled in real terms to its present £3.4 billion ($6.7 billion). Among other things, that money paid for the new £380 million Diamond synchrotron, which began operating in January and is the biggest new U.K. research facility in 40 years. "There's a lot more of a positive feeling now in the whole scientific endeavor," says geneticist Robin Lovell-Badge of the National Institute for Medical Research in Mill Hill.

The scientific community has been impressed that Blair listens to them, especially in a crisis. His government first called on researchers for help in 2000 when foot-and-mouth disease was detected on British farms, threatening the nation's agricultural industry. Newly appointed Chief Scientific Adviser David King, a chemist from the University of Cambridge, was instrumental in enlisting academic epidemiologists, who recommended speeding up the preventive culling of millions of sheep and cattle. Neil Ferguson of Imperial College London, who was involved in the effort to model the disease's spread, says that although some government scientists were resistant, the prime minister's office was "receptive to the best scientific advice." The culling slowed the disease, solidifying the link between Blair and researchers. "How science meets policy in the U.K. was fundamentally changed by the crisis," Ferguson says.

Since then, King has worked to have a scientific adviser appointed in every government department that uses research. "There's a growing engagement between government and the scientific community," says astrophysicist Martin Rees, president of the Royal Society, noting that the introduction into Britain of genetically modified crops in the 1990s was not as adeptly handled as the Blair team's recent management of innovations such as nanotechnology and stem cells. Now, says Rees, the government works with bodies such as the Royal Society to frame appropriate legislation and safeguards.

Although stem cell research has stirred strong passions in many countries, U.K. scientists have been able to pursue a relatively steady course. "[The government] has been on the whole very supportive," says Lovell-Badge. "Most people are able to do the experiments they want." Some alarm bells have been rung, however. A Department of Health white paper last year proposed banning some stem cell experiments, including those in which human and animal material is mixed. Embryo researchers hope that their concerns will be reflected in a draft bill to be published in the next few weeks. "Words spoken by Tony Blair have been very encouraging," says Lovell-Badge.

Early in his tenure, Blair's apparent hesitation on animal research caused concern. A policy document produced when the Labour Party came into power suggested that the new government would restrict such experiments and reduce the use of animals. According to Simon Festing, director of the Research Defence Society, this encouraged animal-rights groups, and extremists "went on the rampage," threatening and physically attacking scientists. In 2003, Cambridge abandoned plans for a primate research lab in part because of security fears; the following year work was halted on an animal research lab in Oxford. "People were scared by the relentless campaigns of harassment," Festing says.

Yet the government eventually expanded ▶

laws to target extremists and stepped up police activity; a raid this month, for example, resulted in the arrest of 30 people linked to animal-rights extremism by the police. Blair himself spoke out in support of animal researchers. "A significant number of extremists are now in jail," Festing says. "Confidence in the bioscience community is growing strongly."

There's no such happy ending, yet, for the Labour government's management of science education at schools and universities. Blair's government has poured large sums of money into school buildings and facilities. But schoolteachers' salaries remain low, which has led many science graduates to take better-paying jobs and caused chronic shortages of specialist science teachers. One-quarter of British high schools now have no physics teacher.

In 1997, Blair inherited a university system that was expanding rapidly. But the big growth has not been in science subjects, and some science departments are struggling to stay afloat. Although students in the U.K. pay some tuition fees—a Blair innovation—universities also get a sum per student from the government to cover teaching costs. Over the past decade, some small science departments have struggled to fill student places, reducing their income. As a result, 21 physics departments have closed, and fewer than half of U.K. universities now offer undergraduate chemistry courses (*Science*, 4 February 2005, p. 668). The government finally took pity last year and set aside £75 million over 3 years to increase the per-student fee in lab-intensive courses. It has also provided grants to stimulate interest in sciences among high school students.

There has been criticism over the way Blair's government has funded university research. Science departments receive block grants from the government to cover the overhead costs of their research, and the size of these grants is determined by the quality of the department's research. Every 5 years or so, all science departments are carefully vetted in a process called the Research Assessment Exercise (RAE). But with the most recent RAE in 2001—the only one during Blair's tenure—the funding rules were adjusted to give more money to the very top-rated departments, leaving many others with nothing. Although some say this has helped the best departments compete internationally, it has made the situation worse for struggling small departments. The system "should allow excellence to develop anywhere," says Rees.

Everyone is now looking for cues from Gordon Brown, the financial brain behind Blair for the past decade and now his likely successor. "Brown seems pretty supportive," says Lovell-Badge. "He's provided modest funding increases that have accumulated over the years. I hope these will continue."

–DANIEL CLERY

LIFE SCIENCES RESEARCH

Massachusetts Proposes $1 Billion Plan

Last week, Massachusetts Governor Deval Patrick declared his state's intention to crank up its status as a life sciences powerhouse. Speaking to the Boston convention of the Biotechnology Industry Organization (BIO), Patrick proposed spending $1 billion over 10 years to create a stem cell bank and promote therapies based on RNA interference (RNAi) technology to turn off genes, for which University of Massachusetts (UM), Worcester, researcher Craig Mello won a Nobel Prize last year.

"We think [the initiative] is pretty distinctive from [that of] any other state," says UM President Jack Wilson, calling stem cells and RNAi the "twin pillars" of a proposal that is expected to be introduced shortly to the legislature. Several states, notably California with its $3 billion bond initiative, have new programs focusing solely on stem cells. Some $500 million for the new Massachusetts program would come from taxes, with a similar amount raised by a bond issue. Half the total would be spent on facilities and equipment; $250 million would be tax breaks to the private sector for jobs in the health and life sciences—a field that already employs one in seven Massachusetts workers. The rest will fund research grants, training, and fellowships. Patrick hopes for another $250 million in matching funds from the private sector.

Biowords. Governor Deval Patrick (*center*) talks up his initiative at the BIO convention in Boston.

CREDIT: CHARLES KRUPA/AP PHOTO

A centerpiece of the initiative is a stem cell bank to share with scientists around the world the more than two dozen human embryonic stem cell lines newly generated by Massachusetts scientists. That's more than the total available to federally funded researchers under a 2001 moratorium imposed by President George W. Bush. The bank will be at UM's Worcester campus, which is already planning an Institute for Stem Cell Research and Regenerative Medicine. Wilson says about $66 million is targeted for the stem cell facilities and $38 million for an RNAi therapeutic center, also at Worcester.

Massachusetts stem cell scientists have been champing at the bit for years, frustrated by the opposition of Republican former governor Mitt Romney to destroying embryos for research. In 2005, the state legislature overrode Romney's objections to research cloning, or somatic cell nuclear transfer.

Patrick, a Democrat elected in November, hopes the initiative will also help researchers hurt by the funding slump at the National Institutes of Health (*Science*, 20 April, p. 356). Harvard University spokesperson Kevin Casey says the package would provide "bridge funding" for people suffering grant delays and also fill "high-risk holes" that venture capitalists avoid. "I give the governor all the credit for this," says Casey.

Administrative details are yet to be settled. But Wilson says the Massachusetts Life Sciences Center at UM Boston, which will be expanded under the initiative, will supply the hub for creation of various mechanisms, such as peer-review groups.

–CONSTANCE HOLDEN

ANCIENT DNA

No Sex Please, We're Neandertals

COLD SPRING HARBOR, NEW YORK—Did Neandertals and modern humans interbreed? Last year, that question took on new life when two groups of researchers reported the first results from sequencing parts of a Neandertal's nuclear genome. The answer, however, was equivocal: One group reported no evidence of interbreeding; the other reported tantalizing hints of mating (*Science*, 17 November 2006, p. 1068). Now, a paper presented last week at the Biology of Genomes meeting here gives the evidence a strong shove in the direction of the no-sex camp.

The new findings also push back the date that Neandertals split from the human branch of the primate tree by 200,000 years—to 800,000 years ago. And another study shows that this ancient human ranged 2000 kilometers farther east—into southern Siberia—something anthropologists have suspected but not confirmed.

These findings come out of an ongoing effort by Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, to sequence the Neandertal genome. Until last year, researchers had only been able to extract and decipher mitochondrial DNA from Neandertal fossils. But in 2006, Pääbo and, using a different approach, James Noonan of Lawrence Berkeley National Laboratory in California and Edward Rubin, director of the Department of Energy Joint Genome Institute in Walnut Creek, California, sequenced nuclear DNA from a Neandertal bone from Croatia.

Rubin and Noonan found no support for interbreeding in 65,000 bases their group sequenced, a finding in line with conclusions from mitochondrial DNA studies. Pääbo, however, found enough so-called single-nucleotide polymorphisms (SNPs) shared with humans, but not chimps, among the million bases his group sequenced to question that conclusion.

In that study, Pääbo used preexisting databases of human variation. Because those databases focus on common SNPs, Pääbo worried that biases might skew the analysis. So David Reich of Harvard Medical School in Boston and James Mullikin of the National Human Genome Research Institute in Bethesda, Maryland, have now compared SNPs in new Neandertal sequences to random SNPs obtained from one African and from one European. The result: "There's no indication of gene flow," Pääbo reported. Pääbo and his group got the same result when they examined variation in the Y chromosome, looking for signs of *Homo sapiens* DNA embedded in the Neandertal sequence.

It may never be possible to prove beyond doubt that interbreeding did not occur. "But if I were to make a guess, I would say more sequence will just confirm [these results]," says Noonan. "It convinces me."

DNA donor. This Croatian fossil is part of the Neandertal genome sequencing project.

CREDIT: SVANTE PÄÄBO

Last year, based on comparisons with the human and chimp genomes, Pääbo's group estimated that Neandertals split off from the human lineage about 600,000 years ago. But they have since found that that estimate changes by 400,000 years depending on the order in which they match up each species' sequence. A new three-way comparison that doesn't give one pairing priority over another comes out at 800,000 years, Pääbo and his Max Planck Institute colleague Richard Green reported at the meeting.

In a side project, Pääbo and his graduate student Johannes Krause have examined 30,000- to 38,000-year-old human fossils from Uzbekistan and the Atlai region of southern Siberia whose identities were a mystery. When the researchers compared the bones' mitochondrial DNA with that from more than a half-dozen Neandertals, they found that the Asian fossils were clearly Neandertal. "It tells us that Neandertals were much more widespread than we thought," says Pääbo.

Neandertals may have roamed far and wide, but when it came to sex, they apparently stuck to their own. **–ELIZABETH PENNISI**

No Smoking, Says California Faculty

Last week, the University of California (UC) faculty senate voted 43–4 against a university-wide ban on tobacco money for research. But antitobacco crusaders haven't given up their 4-year fight. Benjamin Allen, a UC Berkeley law student and future student member of UC's governing body, the regents, is campaigning for a sterner review process for all tobacco industry–funded grants.

Advocates of the ban say that tobacco firms sponsor questionable research and strong-arm fundees. But critics worry that such a ban would curtail academic freedom and threaten other corporate-funded research. The regents put off a vote in January pending the faculty senate's action (*Science*, 26 January, p. 447) and are expected to reject the ban at their July meeting.

Allen's proposal includes an additional level of grant review and a new faculty board to analyze research. Also offered is the chance for individual UC units such as the UC San Diego Cancer Center to ban tobacco money—an action the faculty senate outlawed in 2005. "UC is the only institution in the world that forbids its academic units from declining tobacco money," says Stanton Glantz, a bioengineer at UC San Francisco and a key force behind the proposed ban. Stanford is debating a similar ban and could vote on it as early as this week.

–DAVID GRIMM

Iranians Back Into ACS Fold

The American Chemical Society (ACS) has reinstated 36 Iranian members dumped in January because of the U.S. trade embargo. But ACS will continue to withhold certain member benefits until it obtains a government license.

Although U.S. organizations are prohibited from doing business with anybody in Iran, Cuba, or North Korea, an exemption enables U.S. scholarly societies to have members in those countries. But late last year, ACS officials decided that the full range of membership benefits—which includes discounted journal subscriptions, career counseling, meeting invitations, and insurance—crossed the line.

That ruling drew protest from scores of ACS members. And ACS Executive Director Madeleine Jacobs says she was not part of the decision. "I learned about the move from *Science*," she says (*Science*, 30 March, p. 1777). Last week, the society reversed its decision. But it could be months before ACS obtains a license that would enable it to provide Iranian members with discounted meeting registrations and career-development services.

–YUDHIJIT BHATTACHARJEE

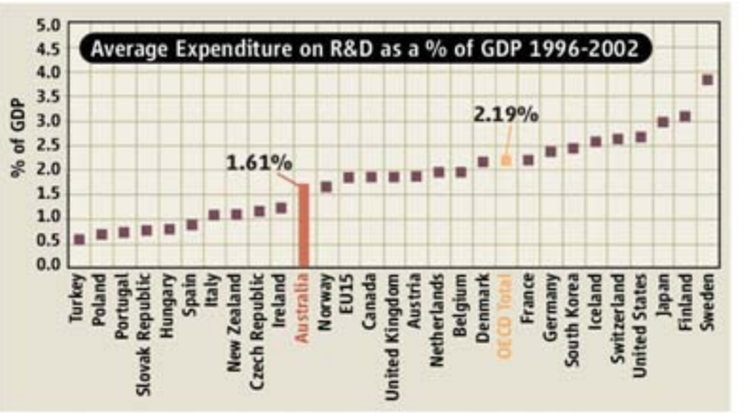
AUSTRALIAN SCIENCE

Universities Are Big Winners in Election-Year Budget

MELBOURNE, AUSTRALIA—Australian universities are getting an antidote to their long malaise: a stunning windfall from a predicted surplus in the 2007–08 budget. The government announced last week that it will deposit $4.2 billion (5 billion Australian dollars)—roughly half the surplus—in a new Higher Education Endowment Fund (HEEF) whose interest would be used primarily to renew crumbling infrastructure at the country's 41 universities.

There was also good news for CSIRO, the national science agency. It will receive $2.3 billion over 4 years: a 19.5% boost over the previous 4 years. CSIRO's record increase includes $43 million for a prototype for the Square Kilometer Array (SKA), a network of radio dishes that would be the largest astronomical instrument ever built (*Science*, 18 August 2006, p. 910). "This is great news," says SKA project scientist Brian Gaensler of the University of Sydney.

Few here expected that higher education would become a campaign issue in the run-up to national elections that must be called by January 2008. Top officials in the Liberal Party have pledged a similar contribution to HEEF next year if their party stays in power; they say they hope ultimately to plow $42 billion into the endowment.



Punching below its weight. A budget windfall will boost Australia's R&D spending, which lags many developed countries (graph depicts averages for 1996–2002).

"It gives universities a profile they've not had for 25 to 30 years," says Gerard Sutton, president of the Australian Vice-Chancellors' Committee.

Australia's universities have struggled for the past decade. The present government had continued a trend of cutting support, with the percentage of university funds from public money sliding from 90% in 1994 to 40% in 2005. Certain disciplines have been hit disproportionately hard. For example, many mathematics departments can't afford to invest in computer labs or retain staff, says the University of Melbourne's Hyam Rubinstein, chair of the Australian Academy of Science's mathematics committee. The new budget allocates an extra $1.4 billion over 3 years to help cover university operating costs. Math departments stand to receive 50% more money per student. "I am hoping this is the beginning of a turnaround," says Rubinstein.

An HEEF board will divvy up this year's estimated $253 million in HEEF interest. Education Minister Julie Bishop has argued that Australia's universities are too homogenous, so the new funds may be used to help establish centers of teaching excellence or tightly focused research institutes. "We would want the projects to reflect the government's call for greater diversity and specialization," Bishop said last week. The science ministry will appoint the HEEF board, which is expected to include the government's chief scientist, Jim Peacock.

–ELIZABETH FINKEL

Elizabeth Finkel is a writer in Melbourne, Australia.

BIOMEDICAL RESEARCH

Temporary Cuts Hit Labs at Child Health Institute

Scientists at the National Institutes of Health (NIH) have been relatively quiet about recent in-house budget cuts—until now. Last week, distress was audible at the National Institute of Child Health and Human Development (NICHD), where officials confirm that lab operating budgets, covering expenses such as research materials and travel, are being slashed by 50% in the remaining 5 months of the fiscal year.

NICHD's 84 principal investigators are now scrambling to keep projects going. "This is one of those danger signals" of long-term troubles, says NICHD cell biologist Bruce Howard, who calls the situation unprecedented in his 33 years at NIH. One scientist who asked not to be identified out of concern for reprisals says his lab is "effectively shut down." Others seem more confident that they can weather the storm.

NICHD Scientific Director Owen Rennert explains that the institute's intramural program got 0.5% less for fiscal year 2007 than last year, or $151 million. Then when final budget numbers came through a few weeks ago, he learned that overall costs would go up 5% to 8%, more than expected, largely because of high winter utility bills on NIH's Bethesda, Maryland, campus. Because personnel costs eat up about half of his budget and staff aren't being cut, that meant much less operating money. Normally, Rennert says, he would use small adjustments to cover a shortfall, such as delaying new hires. But this year, that was not enough. He announced the 50% cut in lab budgets on 4 May.

"It's been a hard week for me, and it is a big cut," Rennert said last week. However, he says that spread out over the entire year, it's closer to 13%. Still, he admits, it means those who spent at a faster rate early in the year are better off.

Scientists say they are now shutting down some studies that use expensive reagents. One investigator says his group is killing transgenic mice; others may pay their own way to meetings. Postdocs nearing the end of their 5-year term may not be able to finish projects that would be important for seeking faculty positions. Judith Kassis said her fruit fly lab will switch from costly molecular projects to genetics work to cope with a budget cut from $29,000 to $14,500. Even so, Kassis feels she may be doing "better than the outside" because "at least we have some money."

NIH Deputy Director for Intramural Research Michael Gottesman says the trend reflects hard times across NIH in recent years, including lab closings at the cancer institute and a 7% reduction in 2006 operations at the diabetes institute. The budget cuts have not changed the fact that NIH "is still a wonderful place to do research," Gottesman says, but "we can't do this forever."

–JOCELYN KAISER

SOURCE: OECD FACTBOOK 2006

ECOLOGY

Savannah River Lab to Close After DOE Cuts Its Funding

Researchers from around the world have come to the Savannah River Ecology Laboratory (SREL) near Aiken, South Carolina, since 1951 to study how nuclear waste can affect habitats and wild populations of bacteria, fish, and reptiles. But this month, the Department of Energy (DOE) lowered the budget ax after deciding that those efforts were "not in line" with the agency's needs in waste management. Now U.S. ecologists are preparing for the demise of the lab itself and the potential layoffs of its 100-member staff, 10 of whom are faculty members at the University of Georgia, Athens, which operates the facility.

The verdant, 803-km^2 Savannah River Site is a multibillion-dollar cleanup area that holds some 140 million liters of Cold War–era high-level weapons waste. It affords one of the largest fenced-in area east of the Mississippi River for ecological studies. SREL's work, says radioecologist F. Ward Whicker of Colorado State University in Fort Collins, "has demonstrated time and again how nuclear activities can be made compatible with maintenance of a high degree of environmental quality."

Two years ago, the lab managed to fend off DOE's attempt to shut it down (*Science*, 25 March 2005, p. 1857). But this year, after DOE pared back funding to $1.8 million from an expected $4 million, lab officials said they would need to close its doors at the end of the month. "We're all shocked," says ecologist H. Ronald Pulliam of the University of Georgia, Athens.

The lab, which got $4.5 million from DOE last year, also receives outside funding, although the extent of that support is under dispute. Last month, DOE said there was "very little evidence" that SREL had sought such funds. But lab director Paul Bertsch says SREL scientists have obtained $5.4 million in multiyear contracts since 2005 and are currently pitching some $15 million in grant proposals to various sources.

DOE and the lab also disagree about the nature of this year's funding. Bertsch says that DOE gave him "verbal agreements" to maintain funding levels. But a DOE spokesperson says no, adding that an internal review of SREL's ongoing studies—including studies of wetlands restoration efforts, metal contaminants, and woodpecker and fish species—compelled the department to limit funds to what had already been spent.

Founded by legendary ecologist Eugene Odum, SREL plays the role of "watchdog" of DOE's Savannah River cleanup, says ecologist Vincent Burke, an editor at Johns Hopkins University Press. Research at the site showed DOE how to save billions in cleanup costs by demonstrating that a contaminated lake habitat could survive without being dredged (*Science*, 12 March 2004, p. 1615). Other studies have looked at how ash from coal plants, which DOE uses to produce power on the site, affects their surroundings.

Outside researchers who prize SREL's facilities worry that the closure will undermine a broad swath of basic ecology work. Avian ecologist Gary Hepp of Auburn University in Alabama, for example, is studying how incubation practices among wood ducks on the site affect development of their young, using a grant from the National Science Foundation. "It's isolated; you don't have people interfering with your sites [or] equipment," says Hepp, noting that SREL staff facilitate access to the heavily guarded Savannah wilderness.

Bertsch is now trying to dispose of lab chemicals and transfer some of the animals on the site. He fears that time will run out, however, before he can raise enough money to continue operations. **–ELI KINTISCH**

Hot zone. A budget crunch has doomed jobs at the Savannah River Ecology Laboratory, whose researchers are shown here sampling radioactive soil.

CREDIT: SAVANNAH RIVER ECOLOGY LABORATORY

Foreigners Welcome, Bush Aide Says

The Bush Administration appears to have thrown its weight behind a proposal to grant automatic green cards to foreign students graduating from U.S. universities with Ph.D.s in science and engineering. Speaking earlier this month at the annual S&T Forum of AAAS (publisher of *Science*), presidential science adviser John Marburger noted that it is "foolish to send [foreign Ph.D.s] home when we want to take advantage of their training and they often want to stay." The proposal is contained in a comprehensive immigration reform bill that is scheduled for debate in the Senate this week and could get a vote in the coming weeks. (A similar bill passed the Senate last year but died in the House due to its guest-worker program.) Backers of high-tech immigration say Marburger's stance is the strongest Administration endorsement yet of opening the doors wider to foreign talent.

–YUDHIJIT BHATTACHARJEE

House to Spies: Investigate Skies

The House of Representatives wants the U.S. intelligence community to consult with climate scientists next year to prepare a report on how climate change will affect American global security interests. The measure, passed as part of a yearly authorization of intelligence programs, drew objections from Republicans who worried about its cost. Representative Mike Rogers (R–MI) suggested that studying "bugs and bunnies" would duplicate existing efforts and could damage morale. Democrats cited a report last month from 11 retired generals who said that climate change is a "threat multiplier for instability" in volatile areas.

The legislation now moves to the Senate. National Intelligence Director Mike McConnell wrote Representative Anna Eshoo (D–CA) last week that he likes the idea. But he thinks that requiring such reports would set a bad example.

–ELI KINTISCH

Under the Umbrella, Everyone

Particle physics in Germany received a $95 million windfall this week with the creation of the Helmholtz Alliance. The umbrella organization, launched by the Helmholtz Association, Germany's publicly funded research behemoth, will support 50 new full-time positions for particle physics research and engineering across the country and a new computing center at the German Electron Synchrotron (DESY) in Hamburg for analyzing data from the particle accelerator at CERN in Switzerland.

–JOHN BOHANNON

The Case of The Empty Hives

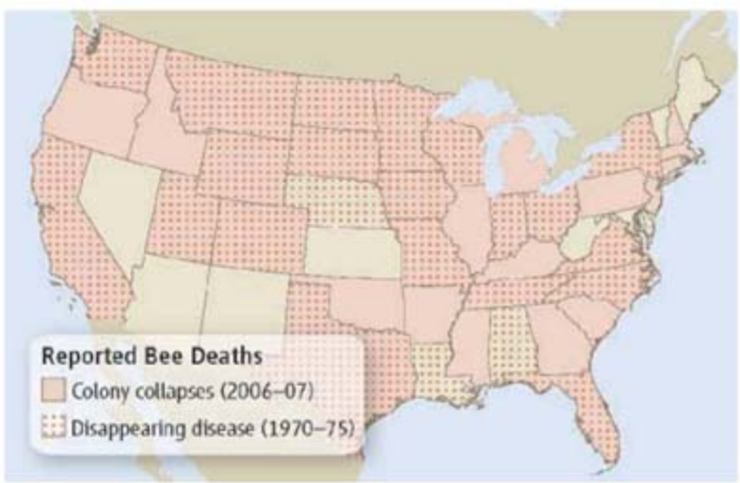
Honey bees worldwide are abandoning their hives, and scientists aren't sure whether to blame pathogens, pesticides, or the artificial diets fed to the bees. It's not even clear if the phenomenon is new

DAVID HACKENBERG WAS THE FIRST beekeeper to draw attention to what is now one of the hottest problems in agriculture: a devastating collapse of honey bee colonies. Last October, while inspecting 400 of his company's hives in Florida, he noticed that 368 were almost empty, despite having been healthy just 3 weeks earlier. Gone were the swarming worker bees; instead, the eerily quiet hives housed just the queen bee and many doomed brood. All told, Hackenberg has lost 85% of his 3000 hives—and $450,000 of income. Although beekeepers are used to abandoned hives and bee die-offs, the extent was far worse than Hackenberg had ever experienced—and he has tended bees for more than 4 decades. "It's probably the most stressful year of my life," he says.

Alarmed, Hackenberg contacted Diana Cox-Foster, an entomologist at Pennsylvania State University (PSU) in State College. Soon she and Dennis vanEngelsdorp, the state apiarist, heard of similar problems from beekeepers across the country. By January, the two had established a network of researchers from Florida to Montana to solve the puzzle of what they're calling colony collapse disorder (CCD). "It's a science-fiction scenario come to life," says entomologist May Berenbaum of the University of Illinois, Urbana-Champaign.

Last year, Berenbaum led a National Research Council panel that warned of a looming pollination crisis if honey bees and other pollinators continue to decline in number (*Science*, 20 October 2006, p. 397). Some scientists now fear that the emergence of CCD will tip the balance, forcing many beekeepers out of business and raising costs for farmers who already rent hives because of a lack of natural pollinators. "We may be near the point when there are not enough bees," says Danny Weaver, a queen breeder with B. Weaver Apiaries in Navasota, Texas.

At a recent meeting to devise a research strategy on CCD, scientists debated whether known bee killers, including pesticides, the varroa mite, viruses, and bacteria, were responsible. Others suspect a novel pathogen, and several top virologists are analyzing samples from afflicted hives at a breakneck pace. Researchers have even irradiated honeycombs to determine whether an infectious agent explains the disorder. Yet some blame the collapses on better understood problems, such as spells of bad weather that leave bees hungry. Or perhaps industrial-scale beekeeping—in which hundreds of thousands of hives are trucked around the country and pumped up with sugar syrups to boost their numbers—has made colonies more vulnerable.



Déjà vu? Beekeepers across the country have reported colony collapses. A mysterious syndrome, called disappearing disease, struck similarly in the 1970s.

Little consensus about the cause of CCD emerged at the meeting, which the U.S. Department of Agriculture (USDA) in Beltsville, Maryland, convened. It could be a variety of factors, notes Jeffery Pettis of the USDA bee lab in Beltsville, Maryland: "At this point, we're proceeding not knowing which causes might be more important." In fact, given that there are so few data on the health of domesticated honey bees—and even fewer on wild populations—many scientists aren't even convinced yet that what's going on is really a new phenomenon.

In decline

Honey bees are indispensable farmhands, pollinating some 95 kinds of fruits and vegetables grown in the United States. An estimate by Cornell University researchers in 2000 placed the value of the insects' services at $14.6 billion in extra yield and improved crop quality. Yet honey bees, like other pollinators, have been in trouble for a while. The number of U.S. honey bee colonies fell from 5 million in 1940 to 2 million in 1989, a decline largely attributed to economic shifts in farming.

For the last 20 years, the biggest issue for beekeepers has been the varroa mite, first noticed in the United States in 1987. Once infected, an untreated hive can be totally wiped out in a few months. "Varroa mites are public enemy number one for bees," says Pettis. The mites have nearly eliminated feral colonies of honey bees, which used to pollinate many vegetable crops. Many farmers must now rent bees for pollination, which has contributed to the growth of large-scale beekeeping; since the late 1980s, the number of colonies has expanded by 25% to 2.5 million.

But now CCD threatens to erase that small comeback—and with lightning speed. Although bees occasionally abandon their

SOURCE: BEE ALERT TECHNOLOGIES; WILLIAM WILSON AND DIANA MENAPACE, *AMERICAN BEE JOURNAL*, MARCH 1979

Scrutinized. Scientists are probing the enigmatic disappearance of worker bees, with brood and queen left behind (*right, bottom*). Parasitic mites (*right, top*) could be a factor.

CREDITS (TOP TO BOTTOM): AP; DENNIS VANENGELSDORP

hives if disturbed, the demographics of these recent collapses are odd. The queen usually remains, surrounded by untended brood. And other insects, such as wax moths or small hive beetles, don't rob the abandoned hives of honey or nectar, suggesting some sort of contamination. "It's bizarre," says Berenbaum.

Puzzling sudden losses of bees have happened before. In 2004, beekeepers had trouble with struggling hives sent to California for pollinating almond trees. And in the 1960s and '70s, before the arrival of mites, beekeepers around the country reported disappearing bees. "It sounds for all the world like what happened last year," says Eric Mussen of the University of California, Davis. Even an article in a bee journal from 1897—long before synthetic pesticides—describes healthy hives collapsing within a week, with the queen still there.

Severe bee losses do appear to be a widespread problem (see map, p. 970). Some 29% of 577 beekeepers across the country reported CCD and losses of up to 75% of their colonies in the last 16 months, according to a survey run by Bee Alert Technology in Missoula, Montana. Losses range from 35% to 100% of hives in each operation. Other countries are also having problems with rapid losses of wild and domesticated honey bees. In Europe, beekeepers from Spain to near the Arctic Circle are reporting deaths or disappearances of their insects, but the symptoms aren't exactly the same as in the United States.

Still, honey bee researcher Nicholas Calderone of Cornell University says it's not clear that these collapses are something other than normal losses. "We're getting a lot of reports of CCD that are not narrowly defined," says entomologist Robert Danka of the USDA bee lab in Baton Rouge, Louisiana.

Rogues' gallery

Assuming that something new is occurring, researchers since January have investigated the usual suspects, including pesticides and other environmental chemicals. The main focus of Cox-Foster's working group is on nicotine-based compounds called neonicotinoids, which were first introduced as pesticides in 1992. One idea is that low doses interfere with a bee's ability to navigate back to the hive. And lab studies have shown that at least one such compound, imidacloprid, can kill bees at high doses.

There are few data that imidacloprid harms bees in fields, however. And other lines of evidence argue against blaming these pesticides. In 1999, France banned imidacloprid after beekeepers complained that it was causing up to 40% of their colonies to die. Yet the colonies don't seem to be doing much better now, notes Yves Le Conte of the Laboratoire Biologie et Protection de L'Abeille, INRA, in Avignon, France.

And in the United States, there has been no spike in imidacloprid usage that might account for the recent colony collapse. "Pesticides can't be an explanation for why organic beekeepers are losing their colonies," Berenbaum says. The CCD working group has nevertheless sent samples of wax, honey, and pollen from hives to be tested by USDA food-testing labs for more than 200 chemicals, including fungicides, pesticides, and their metabolites.

To assess whether pathogens explain CCD, Cox-Foster and her colleagues have collected samples from Pennsylvania of bees remaining in collapsed hives, as well as bees from nearby hives that were healthy or declining. USDA researchers also went to California to get bees from afflicted hives; all told, members of the working group have begun to examine samples from more than 200 hives.

At the meeting, Cox-Foster presented some initial results. "We were shocked by the huge number of pathogens present in each adult bee," she says. The highly diverse array of teeming pathogens included bacteria that cause a condition known as American foulbrood, which turns bees gooey and smelly, a fungus that causes a disease called chalkbrood that turns the insects into white mummies, and four kinds of viruses.

Some researchers suspect that an infectious agent may be spreading between hives via the wax combs and other equipment used by beekeepers. In February, Pettis and his colleagues took combs from CCD-affected colonies in Florida and gamma-irradiated or fumigated some of them before inserting the combs into

hives with mite-free bees imported from Australia. Six weeks later, the scientists counted the number of missing brood cells as a measure of colony health. Because the hives with the irradiated combs had fewer missing brood than ones receiving untreated combs had, Pettis suspects pathogens as a possible cause of CCD.

Adding to suspicions that one or more new pathogens are behind CCD are the results from a team led by Ian Lipkin of the Mailman School of Public Health of Columbia University, which has been doing high-throughput DNA sequencing of bulk bee samples from strong, weak, and recovering colonies. The bees from CCD-afflicted colonies have bacteria, fungi, viruses, and parasites that don't match any known bee pathogens and are not in the healthy colonies, Lipkin says. Cox-Foster suggests that the discovery of so many kinds of pathogens in the collapsed colonies indicates that the bees in them, for whatever reason, have suppressed immune systems.

Yet contradictory results have just come in from bee researcher Jerry Bromenshenk of the University of Montana, Missoula, and Bee Alert Technology and his colleagues. In December, they collected samples from hives in Florida. Preliminary analysis by researchers at the U.S. Army's Edgewood Chemical Biological Center in Maryland found similar viral burdens in healthy, failing, and collapsed hives. "It doesn't seem to fit the idea of a suppressed immune system," Bromenshenk says.

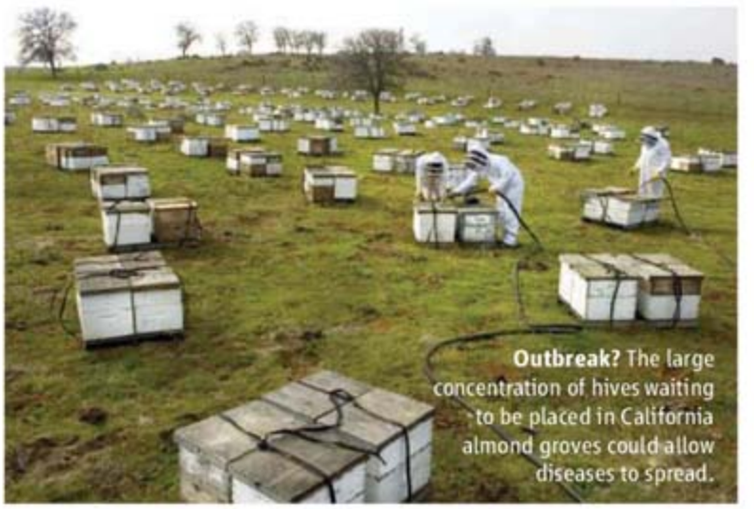
Perhaps the most obvious suspect for CCD, the varroa mite, was also a matter of debate at the Maryland meeting. Mites don't seem to be the main problem, at least in California, says Pettis, because the weak colonies on average didn't have more mites than the strong colonies had. But others argued that mites shouldn't be ruled out yet. Marla Spivak of the University of Minnesota, Twin Cities, cautions that even if beekeepers eliminate a mite infestation, weakened colonies may be set to collapse later.

Dangerous diet?

Modern beekeeping itself, some suggest, puts the insects at risk. In the past 2 decades, as the United States started importing cheap honey from abroad, large beekeeping operations began to make more of their income from renting hives to farmers. California's almond growers, for example, pay a premium rate for pollination.

For bees, that means annual trips to California's central valley, where spring starts early and can be cold and damp. In October and November, more than 1.2 million colonies are trucked into California from all across the country and put into holding yards. Hives are normally inactive during this time of year. But the colonies need to be jam-packed with bees when placed into the flowering almond groves in February, so beekeepers feed them a high-fructose sugar syrup. "They are trying to totally reset the natural cycle of bees," says Marion Ellis of the University of Nebraska, Lincoln. "It's throwing the bees' rhythms out of whack."

The syrupy diet may impair the bees' health, putting them on the verge of a colony collapse. "We can't raise feedlot bees," Ellis says. Pettis doesn't think the syrup is to blame but agrees that no one has hit upon a perfect nutritional formula yet. Last fall, USDA researchers compared two commercial syrups and an experimental one, all designed to stimulate larger increases in bee colonies for almond pollination. None of the diets did the trick, but the experiment did confirm that bee numbers decreased if the insects weren't fed any supplements.



Outbreak? The large concentration of hives waiting to be placed in California almond groves could allow diseases to spread.

Contaminants in such syrups have also been an issue, Mussen notes. Last summer, beekeepers in California noticed that their syrup smelled and tasted wrong. Lab tests revealed that it had high levels of hydroxymethylfurfural (HMF), a compound that can be toxic to bees. But Hackenberg, who sells supplements, doubts that HMF was the problem. Bees will eat HMF-laced syrup, but last fall they weren't taking in any syrup or pollen supplements at all. "They just wouldn't eat the stuff," he says.

On the road again

Ellis and others suspect that the increased trucking of hives may also cause problems for bees. This concern is in part related to nutrition too; whereas bees in Nebraska, for example, used to spend winters in Texas with excellent forage, now they head for California. An abnormally dry season there means fewer wildflowers and less nectar, which weakens the colonies. Mussen wonders whether that caused the problems for hives in California earlier this year. "As soon as they were taken off the almonds, they started going downhill," Mussen recalls. "They were not big, fat bees; they looked malnourished."

Ellis speculates that the physical movement of hives from state to state disturbs the colonies. And placing vast numbers of colonies in one part of California raises the risk of spreading diseases, he says. Mussen agrees on the latter possibility but points out that hives have been trucked around for many years, making that an unlikely explanation for the recent spurt of colony collapses.

The working group is testing the role of shipping using colonies from three large beekeeping operations. Two, including Hackenberg's, were hit by CCD, and one wasn't. In the experiment, 140 hives are staying in one place for honey production, while another 140 are being moved five times for various pollination jobs. At each point, bees will be sampled and sent to PSU and USDA for pathogen analysis.

Researchers at the Beltsville meeting agreed that the immediate top priority is better surveillance to establish the true incidence of colony collapse. They called for a $2 million survey of bee health by USDA's Animal and Plant Health Inspection Service, which the agency had proposed last year but was not funded. Ultimately, researchers want to be able to predict and then prevent CCD. "We need practical bioassays for beekeepers—and to be able to tell them what to do in response," says vanEngelsdorp.

Despite the recent colony collapses, almond growers expect a bumper crop this year, says Marsha Venable of the Almond Board of California. But they've had to raise their payments for renting hives from $50 a colony a few years ago to $120 this spring. And with another 40,000 hectares of young almond trees that will need pollination in the next few years, the price will only go higher if the riddle of the abandoned hives isn't solved. Beekeepers, Pettis says, "aren't going to meet the demand without something changing."

Indeed, Hackenberg, who has spent the past months trying to rebuild his colonies, worries that another year like this one will put him out of business: "This is do or die."

–ERIK STOKSTAD

CREDIT: RANDY PENCH/MCT/LANDOV

PROFILE: SUSAN DUDLEY

New Regulatory Czar Says Rules 'Should Make People Better Off'

Critics wonder how free-market economist Susan Dudley will apply her cost-benefit analysis to federal regulations

Susan Dudley, the new White House czar of regulation, calls it her "dream job." It's a homecoming of sorts: 20 years ago, during the Reagan Administration, she worked as a staff economist in the Office of Management and Budget's Office of Information and Regulatory Affairs (OIRA). She is now OIRA's administrator, with the power to review all proposed U.S. government regulations.

But Dudley, 51, returned to the White House last month via the side entrance. Her nomination last summer by President George W. Bush enraged environmentalists and consumer advocates. For the past 4 years, as head of regulatory studies at the Mercatus Center of George Mason University in Fairfax, Virginia, she's been a vociferous critic of many federal regulations, usually arguing that their costs outweigh their benefits. Two groups, Public Citizen and OMB Watch, called her "an antiregulatory zealot with close ties to corporate interests." After the Senate refused to consider her nomination, Bush sidestepped the confirmation process and appointed Dudley during a congressional recess. That allows her to serve through the next session of Congress, most likely through the waning days of the Bush presidency.

"My own style is collaborative. It certainly does not need to be antiagency."
—Susan Dudley

Dudley is widely regarded as personally likable, even charming. As evidence of her "personal commitment to environmental stewardship," White House officials touted the fact that she and her husband, a top official at the Environmental Protection Agency, drive to work in a hybrid car. They neglected to mention, however, that it's an hour commute from a historic mill town near Warrenton, Virginia.

In an 18 April interview, her first since taking office, Dudley was careful to avoid further controversy. She declined to criticize current regulations or comment on possible new ones, such as limits on greenhouse gas emissions under the Clean Air Act. Her job, she said, is "to implement the law of the land."

Insider now. Susan Dudley brings her record of criticizing federal regulatory policy to the White House.

CREDIT: GREG SCHALER

On her goals

"A lot of what OIRA does is reactive. We evaluate agencies' regulations. I want to make sure that those regulations, within the constraints that we have, are based on the best available evidence, that they go through open and transparent public comment, that the process and the analysis on those regulations is the best that it can be. One of the things that happens at the end of [any] administration is the "midnight regulation" phenomenon. Regardless of

Decision on Lead Emissions Weighs Heavily on EPA

The latest regulatory controversy heading toward Susan Dudley's inbox involves the toxic legacy of lead pollution. At the center of the controversy is Dudley's favorite theme: costs versus benefits.

Lead is one of six major pollutants covered by the Clean Air Act, but levels of lead in the air have fallen dramatically since it was removed from gasoline in the 1970s and 1980s. Rarely do air-pollution monitors anywhere detect levels above 1.5 $\mu g/m^3$, the Environmental Protection Agency's (EPA's) current "ambient air quality standard." EPA is currently reviewing that standard and expects to have a new one in place by the end of next year.

Last fall, the lead battery industry suggested that EPA declare victory in the battle for lead-free air and stop regulating it under the Clean Air Act. On 27 March, however, EPA's scientific advisers urged exactly the opposite. They unanimously called for a drastic tightening of the agency's air-quality standard for lead, lowering the permissible level to 0.2 $\mu g/m^3$. Bruce Lanphear, director of the Cincinnati Children's Environmental Health Center in Ohio and a member of the EPA panel, says that scientists were persuaded by recent studies showing lowered IQ among children exposed even to tiny amounts of lead. Some members of the panel proposed an even stricter standard of 0.025 $\mu g/m^3$.

Such a tight limit would face stiff opposition. David Weinberg, a lawyer who represents Battery Council International, an industry group, says that air along many old and heavily traveled roads sometimes exceeds this standard because lead deposited in the soil decades ago is stirred up by passing traffic. "The only realistic way to meet this standard would be to treat, dig up, or cover the roadsides," he says.

In her interview (see main text), Dudley said she "hadn't heard" about the issue. But one of her former colleagues and collaborators, Andrew Morriss, now a professor of law and business at the University of Illinois, Urbana-Champaign, says the proposed lead standard touches on some problems she often raised with regulations. EPA's science panel didn't consider the cost of a tighter limit on lead in the air, he says, "but when you don't have information on cost, you can't prioritize anything." Morriss says it's likely that more children could be protected from lead, at a much lower cost, by renovating old houses rather than eliminating contaminated soil from along the road.

Current laws, however, don't authorize such comparisons, which limits Dudley's power to change policy. "Her hands are tied in many respects," says Morriss. **–D.C.**

party, you see an increase in regulation.

"I probably can't say that we won't have an increase in regulatory activity. But they won't be slipshod, dashed out at the last minute. They will have gone through careful review … to make sure that they really make people better off and not worse off; that they serve a broader public interest and not a narrow interest."

On regulatory burdens

"I would say that there are better ways to do regulations. We can regulate smarter, get the benefits that we all desire, with fewer costs.

"I did my master's thesis on economic incentives for pollution control. Back then, it was a novel idea. In the 1970s and early '80s, command and control [legal limits on pollution, enforced by fines or criminal penalties, as opposed to economic measures such as taxes or tradable pollution permits] was the standard approach to addressing environmental problems. Now, it's 'How can we harness market incentives?' People realize that if you provide incentives, you can reach the outcome you intended. Command and control doesn't always reach that outcome. If you force people to do something, but they don't really want to, they'll find ways to meet the letter of the law, but you might have some unintended effects."

On other regulatory agencies

"OIRA is a bit of a watchdog. I don't think it's antiagency. A lot of what we do is interagency coordinating, … making things more transparent, and that's not always welcome. I was here for 5 years. My experience is, it's actually quite collaborative. My own style is collaborative. It certainly does not need to be antiagency."

Comparing the Reagan and Bush years

"I think that the focus now is more on regulatory reform, or smarter regulation. Back then, the phrase was 'regulatory relief.' Now you won't see that phrase. You'll see people talking about smarter regulation."

On OIRA's proposed risk-assessment guidelines

"What [the recent National Academies report] said was, 'We agree with your goal. We don't think you got it quite right.' There were very constructive suggestions in the report. I think there is something we can do to meet everyone's goal. I think there is a path forward, to rationalize the risk-assessment process and coordinate across agencies."

–DAN CHARLES

Dan Charles is a freelance science writer based in Washington, D.C.

Reaching new heights. Wolong Nature Reserve bred a record number of pandas last year.

CREDIT: CHARLOTTE JENNINGS

WILDLIFE CONSERVATION

Giant Panda Numbers Are Surging—or Are They?

Experts are sparring over a controversial count of wild pandas and plans to expand captive breeding of China's revered symbol

WANGLANG NATURE RESERVE, CHINA—The excited cry of a park ranger pierces the stillness of a bamboo forest high in the Min Mountains. Zhan Xiangjiang, an ecologist with the Institute of Zoology in Beijing, bounds through waist-deep snowdrifts to investigate. Catching up with the ranger, he kneels down and points at a small, round object that, at first glance, looks like a greenish yam. "Smell this!" he exclaims. The not-unpleasant odor of fresh bamboo wafts up. Along with other clues—chewed bamboo stalks, paw prints, and urine-marked trees—the fresh scat is the latest evidence that Zhan's monitoring team is hot on the heels of a giant panda.

Their quarry may be elusive, but Zhan is upbeat. "Pandas are making a comeback here," he declares. In the mid-1980s, poaching and a mass bamboo die-off sent China's flagship animal into a tailspin: The country's wild panda population plummeted to about 1200, landing the species on the endangered list. Experts decried its imminent extinction. But with a logging ban in all panda habitats since 1999, the species appears to be on the rebound.

It is a hotly debated question, however, whether panda populations are just beginning to regain lost ground or are already healthier than they have been for many years. Using DNA from hundreds of scat samples collected in Wanglang, Zhan and colleagues published a paper last year in *Current Biology* (20 June 2006) claiming that China may have 3000 wild giant pandas—a doubling in less than a decade since the previous survey. The rosy analysis has been vigorously contested. "It frankly seems preposterous" that panda numbers have grown that rapidly, says David Garshelis, Bear Specialist Group co-chair for the World Conservation Union (IUCN). Wanglang scientists defend their robust figure. "The situation [for pandas] has really improved," says Wanglang reserve vice-director Jiang Shiwei. "We've seen a population increase, with newborns every year."

Virtually nothing about the iconic mammal is without rancor. Another controversy swirls around China's program to breed giant pandas in captivity. Last year, the effort produced more than 30 cubs—a record—as well as the first captive released into the wild. Some conservationists say the breeding program can bolster wild populations. Others are skeptical. "The key is to protect the habitat, not reintroduce more pandas," says Lu Zhi, director of the nonprofit Conservation International's China office. "They can breed themselves, and it's a reasonable population already, so why add another flower to the garden?"

Arguable estimates

Zhan cups some scat in his bare hand and grins as it shimmers in the sunlight. "The shiny layer is mucus," he says—and it's full of DNA. To

gauge how many pandas are prowling Wanglang, Zhan spent much of 2003 and 2004 combing the area for precious panda droppings. His zeal almost got him killed—in 2004, he slipped and broke his spine and had to endure a bumpy 400-kilometer ride to a hospital in Chengdu, the capital of Sichuan Province. He was not paralyzed, however, and returned to work after a 3-month-long convalescence.

Zhan's team extracted DNA from the mucus in 2005 and used genetic markers called microsatellite loci to identify individuals. Based on this DNA-fingerprinting technique, Zhan says there are at least 66 pandas in Wanglang—a big jump over the 27 estimated in the Third National Survey. That census, in 1998, employed the traditional bamboo-fragment method, which differentiates individuals by comparing the lengths of chewed bamboo in scat. Zhan argues that the bamboo fragment method's total of 1596 pandas in China's 60 panda reserves lowballed the actual population size. "We found the population is much more than we thought in the past," says the Institute of Zoology's Wei Fuwen, senior author of the *Current Biology* paper.

In an unpublished letter to *Current Biology*, Garshelis and five colleagues expressed doubts about Zhan's analysis. "Our concern is that it's jumping the gun," says Garshelis. "They only have one data point [Wanglang], which they extrapolated to the entire range." And that data point is suspect, he says. Garshelis thinks that Wanglang simply can't support that many pandas; according to Zhan's estimate, one section of the reserve has two pandas per square kilometer—the highest recorded density for any bear species.

A population doubling at Wanglang is impossible, argues Wang Dajun, a panda researcher at Peking University, because habitat there shrank steadily until at least 1998, when the logging ban was enacted. By comparing satellite images from 1990 and 2000, Wang quantified a heavy degree of deforestation that, he says, must be harmful to pandas. Jiang agrees that habitat fragmentation imperils panda populations in smaller, isolated reserves—but not Wanglang.

The uncertainty means the giant panda will remain classified as endangered in an IUCN report slated for release later this year, the first panda update in a decade, says Garshelis. "I get the feeling the population is slowly growing," he says. "But until there's better evidence, there's certainly no reason to remove pandas from the endangered list."

Growing pains

On a single-lane dirt road wending between misty crags deep in Sichuan Province, traffic has slowed to a crawl. Hundreds of dump trucks and steamrollers are expanding the only road to Wolong Nature Reserve into a modern freeway. Conservation biologist George Schaller of the Wildlife Conservation Society in New York City was the first Westerner to study giant pandas in China when he came to Wolong, about 500 kilometers southwest of Wanglang, in 1980. Now, more than 100,000 tourists every year flock to Wolong, the country's most famous panda reserve, to see its 120 captive-bred pandas, the largest such population in the world.

Cut to shreds. Panda habitat today covers a tiny fraction of the bear's historic range.

SOURCE: COLBY LOUCKS/WORLD WILDLIFE FUND

More captives would be better, argues Wolong Director Zhang Hemin, who is aiming for 300 within the next decade. A population of this size, he says, could ensure the panda's survival for the next century while retaining 95% of its genetic diversity.

A decade ago, the captive birth of a single cub would cause a huge media sensation. Back then, if a mother bore twins, she would invariably abandon one and raise the other. In 2000, breeders figured out how to raise twins by allowing one cub at a time to stay with the mother and raising the other by hand. They frequently swap cubs so both learn survival lessons from mom. Now Wolong is trying to outdo last year's record number of births by artificial insemination.

Not everyone is handing out cigars. Lu argues that Wolong's ambitions may divert funds from conservation programs aiming to protect wild populations. "Maintaining a captive population is not cheap, so they seriously need to ask themselves why they need 300 pandas," she says.

Zhang defends the target. Wolong's goal, he says, is to introduce 10 to 20 captive pandas a year to shore up smaller wild populations. In April 2006, Wolong staff for the first time released a captive: Xiangxiang, a mild-mannered 5-year-old male. He was so badly mauled by a wild male last December that rangers had to treat him at the reserve's "panda hospital" before releasing him back into the wild. Then in late March, rangers found Xiangxiang dead; apparently he had fallen from a tree after clashes with other pandas, says Zhang. "The reintroduction program is very difficult," he admits. But he will not be deterred: Wolong plans to release another bred panda within the next 5 years.

Panda experts agree that the species needs all the help it can get. Tourism and development are nipping at the reserves. Tourists leave garbage, and villagers lay traps for game animals that inadvertently snare pandas, says Lu. Conservation International is testing a new community-based conservation model this year that will give villagers financial incentives to protect panda habitat outside the reserves. Three villages abutting Wanglang have signed on, and negotiations are under way to add 100 more sites in the next 3 years.

The central government, too, is taking action. Its Wildlife Conservation Protection Program seeks to bring 90% of wild pandas under the reserve system, from 75% today. In the 1980s, there were fewer than 20 reserves for pandas. Now there are 60. "The State Forestry Administration is putting a lot of money to set up this panda reserve network," says Wei, who notes that two or three reserves are added each year, on average.

Down from the mountain, Zhan's monitoring team encounters a pair of blue-eared pheasants, their most dramatic wildlife sighting all day. No black-and-white bamboo eaters—but that's not necessarily a bad thing, says Zhan. It means the pandas are somewhere in the highlands, deep in the bamboo forest, and safe from humans for another day.

–JERRY GUO

Jerry Guo is a writer in New Haven, Connecticut.

PSYCHIATRIC RESEARCH

Putting the Brakes on Psychosis

A group in Maine is exporting a program that flags young people for therapy before mental illness sets in

PORTLAND, MAINE—Last month, William McFarlane, a psychiatrist at Maine Medical Center here, received an appeal for help as he was leading an informational conference call about psychosis. In a weary voice, barely audible over speakerphone, a mother recounted changes in her teenage son, recently diagnosed with schizophrenia. Once friendly and outgoing, the boy had become isolated, suspicious, and threatening. At times he would retreat to his room and lash out at whoever approached him. The closest psychiatrist was located far from the family's home in rural Mississippi.

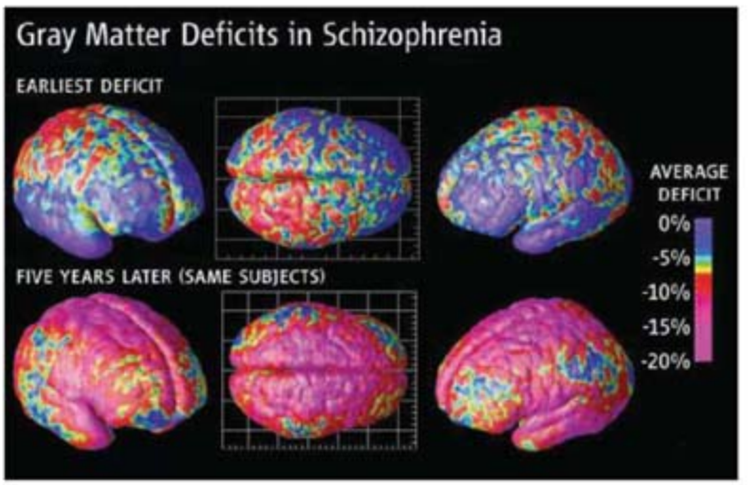
From Portland, there was little McFarlane could do. But his frustration was palpable; McFarlane believes that if caught early enough, psychosis is preventable. Hallucinations, delusions, paranoia, and other symptoms of psychotic illnesses such as schizophrenia afflict more than 2 million people in the United States and account for more than half the suicides among adolescents and young adults.

Now, with a $12.4 million grant from the Robert Wood Johnson Foundation (RWJF) in Princeton, New Jersey, McFarlane is expanding the most far-reaching effort yet to prevent psychosis among those at greatest risk. Launched in 2000, the Portland Identification and Early Referral (PIER) program works with communities in southern Maine to identify the riskiest cases among adolescents and young adults in crisis and prevent them from spiraling into profound mental illness. The 4-year grant awarded last month will allow McFarlane to add four new sites embracing populations of up to 400,000 each—in Sacramento, California; Ypsilanti, Michigan; Salem, Oregon; and Glen Oaks, New York.

The key to PIER's strategy is to identify "prodromal" symptoms that are evident for months or years before psychotic illnesses appear and treat aggressively. Such symptoms include declining school or work performance, jumbled thoughts and confusion, trouble speaking clearly, and hearing sounds that aren't there. PIER trains those who work routinely with adolescents and young adults to recognize prodromal symptoms; up to 17 school districts in greater Portland are involved, as are health care workers.

Although telltale signs typically precede psychosis, those signs are also shared by other, more benign conditions, including depression, anxiety, or even adolescent growing pains. As a consequence, only about one-third of the patients who could qualify as prodromal actually develop a psychotic disorder. This high false-positive rate raises the question of whether it is right to deploy therapies—including drugs—as broadly as PIER does.

Patients enrolled in PIER undergo an intense regime of low-dose medication and counseling, aimed at eliminating stressful situations that could trigger psychotic reactions. Family involvement is crucial, as are social networks designed to keep patients in school or at work. McFarlane is convinced that with time, they can overcome—or even outgrow—their vulnerability and remain symptom-free. The positive results in Portland, which McFarlane is preparing for publication, persuaded RWJF to invest.



Decline. Brain scans of a group of teenagers with schizophrenia show a loss of gray matter, suggesting a need for early intervention.

McFarlane's efforts to intervene in psychosis before it happens are unique, says psychologist Dennis Dyck of Washington State University in Pullman: "Most interventions take place after the first psychotic break has already occurred." PIER treats such patients, too, but it stands apart because of its emphasis on prevention and links to the community.

Medication warranted?

The first large test of psychosis prevention took place in the 1980s under the direction of the late Ian Falloon, a professor of psychiatry at Auckland Medical School in New Zealand. Citing growing evidence that a cluster of symptoms could predict schizophrenia—and that the disease itself was triggered in genetically susceptible people by major life events and stress—Falloon proposed that medication and psychosocial supports could reduce the individual's vulnerability to psychotic episodes.

Falloon created a model mental health service in Buckingham and Winslow, two small towns northwest of London, that identified high-risk patients in the community. Caregivers followed up with support services, including education about schizophrenia, home-based stress-management resources, and low doses of antipsychotic drugs. When the study wrapped up 4 years later, Falloon reported in the journal *Psychiatry* in 1992, rates of hospital admissions for psychosis in the treatment zones were one-tenth those in the rest of the country. But because screening methods may not have caught some people who were headed for schizophrenia later, he warned, the results may have overstated the program's effectiveness.

That uncertainty fuels an ongoing debate over how prodromal symptoms should be treated. Mounting evidence suggests that early interventions can delay or prevent psychosis while helping patients lead healthier lives. But both medication and psychosocial methods pose a degree of risk. With psychosocial interventions, says Thomas McGlashan, a professor of psychiatry at Yale University, there is a risk that treating false-positive patients might add stress, making them think they're on the verge of schizophrenia when they're not. "But that isn't something we've seen in our patients," he says.

Antipsychotic drugs, meanwhile, can produce weight gain and metabolic problems, including diabetes. What's more, the drugs might negatively impact the developing adolescent brain. However, Cameron Carter, a professor of psychiatry and neuroscience at the University of Cal-

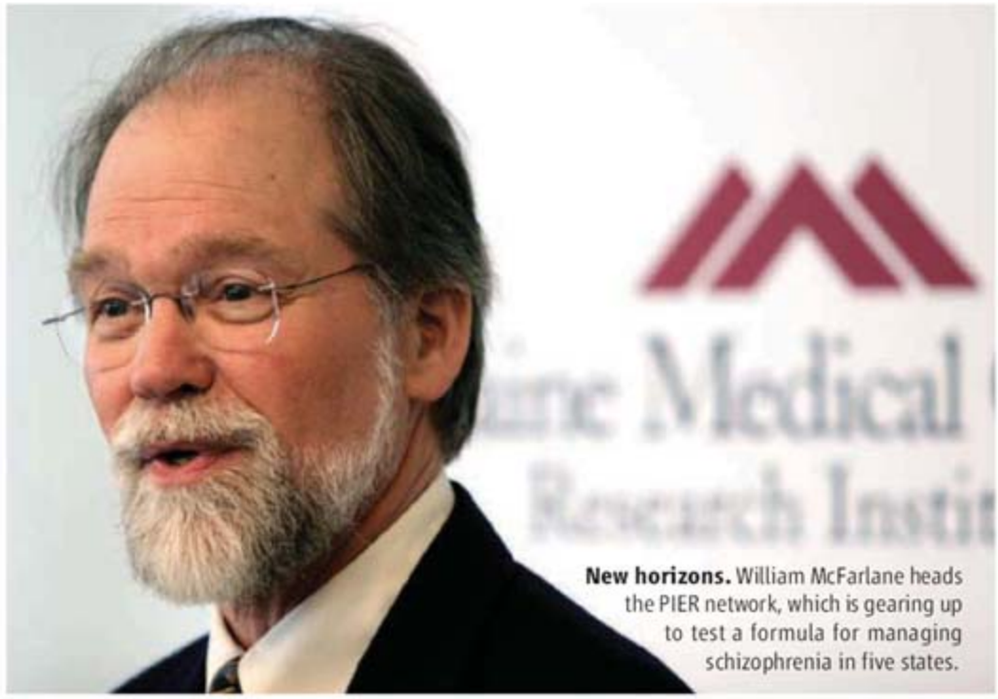
CREDIT: PAUL THOMPSON/UCLA

ifornia, Davis, suggests that those risks could be more than offset by lowering the risks of a psychotic reaction, which itself can be highly damaging, sensitizing the brain to ever more severe hallucinations, delusions, and other psychotic symptoms when under stress.

Still, some researchers insist that antipsychotic drugs should not be given to patients who are not diagnosed as psychotic. "We don't know enough about the risk-benefit ratio," says Diana Perkins, a professor of psychiatry at the University of North Carolina, Chapel Hill, who believes more study of the effects of antipsychotics in adolescents is warranted before a study like McFarlane's moves forward. "So we don't want to expose people who aren't at risk of psychosis to a drug that can hurt them."

Anthony Lehman, chair of psychiatry at the University of Maryland Medical Center in Baltimore, warns against using medication during early prodromal stages but adds that it may be appropriate if the patient appears close to a psychotic break. "It really depends on where you are in the prodromal phase," he says. "That's where the tension in this whole area lies: You have to make decisions based on each case."

Patrick McGorry, a research psychiatrist at the University of Melbourne in Australia, suggests that prodromal interventions should be deployed in stages, starting with psychosocial methods and omega-3 fatty acids (which may have mood-stabilizing effects) as a frontline treatment. "We would reserve medication for when it's clearly indicated," when psychosis is evident, he says.



New horizons. William McFarlane heads the PIER network, which is gearing up to test a formula for managing schizophrenia in five states.

CREDIT: AP

It's difficult to compare the benefits of medication versus psychosocial support because there's so little data, says Jeffrey Lieberman of Columbia University College of Physicians and Surgeons. Of the available studies in preventing psychosis, only one—published by McGlashan in 2006—investigated medication as the sole intervention. That study suggested a drug called olanzapine could cut progression rates to psychosis in prodromal patients by half. However, the results were deemed inconclusive because weight gain and fatigue led to a high dropout rate in the treatment group.

> "That's where the tension in this whole area lies: **You have to make decisions based on each case."**
>
> —Anthony Lehman

In another study, published in 2002, McGorry reported that a combination of medication plus cognitive behavior therapy—a talk therapy that aims to reorder distorted thinking—was more effective at preventing psychosis than psychotherapy alone. Over time, however, several patients in the treatment group became psychotic, diminishing the significance of the initial results. In the only study of psychosocial supports without medication, Anthony Morrison of the University of Manchester, U.K., found in a study of 58 patients that the progression to psychosis could be delayed, or prevented, solely with cognitive behavior therapy. That finding, he wrote in his 2004 paper, "suggests psychosocial intervention … will be an effective and acceptable alternative to antipsychotic medication, particularly for patients at ultra-high risk of developing psychosis."

In McFarlane's view, medication stabilizes patients, enabling psychosocial supports that bolster self-confidence and coping skills to take effect. "I started off as a psychosocial intervention researcher, and when we launched PIER, we weren't going to use medication unless it was absolutely necessary," McFarlane says. "But as it turns out, absolutely necessary was just about every case. I can't recommend we go to a no-medication control. That essentially consigns half the group to inevitable mental illness and psychosis."

Minimizing drugs

For the newly expanded study, McFarlane will consider a staged approach such as that proposed by McGorry—limiting medication only to those who appear at greatest risk. Among the newer drugs used will be aripiprizole, an antipsychotic that shows little evidence—so far—of weight-gain side effects.

Meanwhile, every patient brought into the program will get the psychosocial treatment used in PIER, one that McFarlane started honing 25 years ago at a mental health clinic in the south Bronx, New York. Known as Family-Aided Assertive Community Treatment, the model has two components: The first, called the multifamily group model, unites several patients and their families in group therapy, so they don't have to go it alone. McFarlane has found that the approach helps families cope with the isolation and stigma that comes with mental illness. The second component—Assertive Community Treatment (ACT)—has a long history in the management of psychotic disease. ACT involves schools, employers, and other community elements. Each patient will be treated for a minimum of 2 years, he adds, and some may be treated for four.

As the effort moves forward, hospitalization rates for psychosis in the catchment areas—where early-intervention resources have been made available in a given state—will be compared to those in the rest of the state. McFarlane says: "I'm confident this is going to work; our kids just keep getting better and better. Our experience has been that after a couple of years, they don't need a lot more support." That conviction will soon be put to the test.

–CHARLES SCHMIDT

Charles Schmidt is a writer in Portland, Maine.

Monkey writers. Monkey heads suggest that an entombed Maya ruler may have been a scribe.

Portals to the Supernatural World Uncovered in Mayan Tomb

Deep in the Guatemala jungle, archaeologists have found a 1400-year-old royal tomb with a spectacular array of artifacts, including a carved stele, heirlooms from an earlier civilization, and an unusual set of intact figurines that are dazzling Mayan experts. "The figurines are of quite astonishing quality, and their layout is evidently that of a royal court," says Mayan specialist Stephen Houston of Brown University, who was not involved in the discovery. "It's unprecedented." Such figurines tend to be found in isolation, but the circular arrangement in which these objects were found offers a glimpse into both the political and religious realms of the Maya, says Houston.

The tomb is at El Perú, about 60 kilometers west of the famous Mayan ruin of Tikal in northern Guatemala, which flourished in the centuries before and after Christ. In 2006, during the fourth season of digs at the site, archaeologists led by David Freidel of Southern Methodist University (SMU) in Dallas, Texas, uncovered the remains of a ruler dating to the mid-6th to mid-7th century C.E., a period for which there has been no written evidence until now.

Sacred circle. Maya figurines were carefully arranged around a sacred space.

Along with the two dozen ceramic figurines, the vaulted tomb within the pyramid included a child sacrifice covered with a jaguar pelt, a mosaic mask, 33 ceramic vessels, and two tiny, finely made heads of monkeys, which are associated with scribes. The monkeys may indicate that the El Perú ruler was himself a trained scribe, says SMU archaeologist Michelle Rich, who presented a paper on the find. This and other recent discoveries point to Mayan rulers who were artists and scholars as well as the warrior-kings favored in current popular culture, says Freidel.

The cluster of figurines includes an outer circle representing a king, queen, ballplayer, scribes, and other court members. An inner circle includes an array of creatures that inhabit the world between the real and the supernatural, including a frog, dwarves, and a shaman with a contorted face. Rich speculates that the inner circle signifies a portal both to the supernatural world and to a period before time and may represent a creation myth similar to the one outlined in the Mayan texts of the Popol Vuh. Such portals are a common feature of both architecture and religious texts in ancient Mesoamerica.

Houston says nothing like the El Perú figurines has been found since excavations in the 1950s at La Venta, an important Olmec city that flourished nearly a millennium before the Mayan classic period. The tomb also contained a statue from the Olmec civilization, an unusual discovery suggesting a marked reverence for the distant past.

Archaeologists are eager to analyze these and other treasures from El Perú—which remain at the team's lab in Guatemala City—including two sculptural heads that use imagery from Teotihuacán, a great city far to the north. The heads may even celebrate the arrival of a Teotihuacán warlord in El Perú in 378 C.E. A stele found at the tomb entrance, the first inscription found during this era, likely was erected by a successor king a half-century after the royal burial in about 600 C.E. There may be even more to find: Rich hopes to return to the site for further excavations in 2008.

Climate Spurred Later Indus Decline

Climate change is not just for us moderns. Four millennia ago, a pronounced dry spell settled over much of western Asia, stressing the young Egyptian and Mesopotamian civilizations. But archaeologists have puzzled over the fact that the Indus River civilization, centered in what is now India and Pakistan, was at its height during this time.

Now a team made up of a climate modeler, a geologist, and an archaeologist say they have solid evidence about how climate affected Indus society. They suggest that the Indus people were able to adapt to the immediate climate change, but that resultant shifts in vegetation and landscape eventually set the culture on a slow course of decline. "How people coped varied region to region," says Yale University archaeologist Harvey Weiss, who is not part of the effort. Weiss argues that the Akkadian empire in Mesopotamia collapsed as a result of the dramatic drought that affected societies from Ireland to China.

Previous researchers depended primarily on cores from off the coast of Pakistan and other regional data to understand climate change in the Indus region. But the team also drew on data collected between 1996 and 2001 at the ancient mound of Harappa, one of the principal cities of the Indus, and its immediate neighboring areas. By 2600 B.C.E., Harappa was a thriving urban center. But starting at about 1900 B.C.E.—2 or 3 centuries

CREDITS (TOP TO BOTTOM): MICHELLE RICH; VARINIA MATUTE

Out of the blue. Lapis from Ur may now be sourced.

Snapshots From the Meeting >>

Tracking lapis's lure. Egyptian pharaohs treasured it. Mesopotamian rulers were buried with it. And Indus River craftsmen carved lapis lazuli into myriad shapes for export. The rare blue mineral has been prized since prehistoric times, but scholars have been frustrated in their attempts to use it to track ancient trade networks. Lapis is heterogeneous in its makeup, and traditional methods often failed at sourcing samples. Now, researchers can use mass spectrometry to examine a sample's trace elements and track its origins, says Harvard University archaeologist Irene Good.

Physicist Judit Zsöldföldi of Tübingen University in Germany and chemist Zsolt Kasztovskzy of the Hungarian Academy of Sciences recently subjected modern lapis samples to two techniques: atomic absorption spectrophotometry, which can produce a detailed mineral analysis using as little as one-hundredth of a gram, and prompt gamma ray activation analysis, which can measure mineral content without destroying a sample. The pair identified mineral signatures in lapis from the biggest and most archaeologically relevant quarries, including in Afghanistan, Lake Baikal, and elsewhere.

Applying these methods to ancient lapis is "an important discovery," says Good. It means that lapis in museum objects—such as King Tut's mask from Egypt or the stunning jewelry from the Royal Tombs of Ur in Iraq—may be able to be sourced. The trade in lapis, which dates back more than 5 millennia, could reveal the antecedents of the later silk road from Central Asia to India and Europe, Good says. Her team plans to conduct studies this summer with samples from Tajikistan and Iran.

Searching for inequality. Archaeologists have long assumed that agriculture and social inequality emerged together. Whereas egalitarianism reigned among hunter-gatherers, the thinking goes, agriculture sparked a centralization of power, with one group toiling in the fields while another directed construction of monuments and cities. That inequality can be seen clearly in ancient Egypt and Mesopotamia, where some tombs are laden with gold and gems while others are bare.

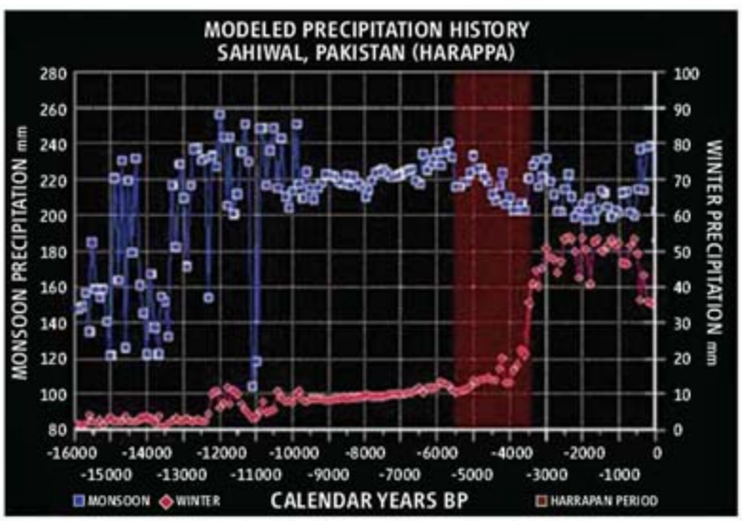
But at an unusual session spanning different periods and places, researchers packed the room to ponder whether hierarchy and social complexity are always visible in the material objects of the archaeological record. Kenneth Ames of Portland State University in Oregon suggested turning to cultural anthropology and primatology for clues. For example, recent studies show that among African pygmies who appear to lack hierarchy in elite goods, some individuals nevertheless have better dental health—a sign that this apparently egalitarian society nevertheless has high-status members with better diets and health. Hunters and gatherers such as the native Americans of the northwest coast can also have clear hierarchies, adds Douglas Price of the University of Wisconsin, Madison, although their material differences are not as distinctive as those of the classic Near East societies. Ames also notes that primate societies show a wide variety of dominance structures, a sign that egalitarianism is not common even among humanity's close cousins.

Even in the Near East, the link between early social inequality and agriculture remains ambiguous, says Ames. The Natufians who lived there at the dawn of agriculture left little clear evidence that some had substantially more power and wealth than others. "Archaeologists rely on exotic artifacts," says Price. "We need more robust indicators in equality, such as dental health and diet."

–A.L.

after the drying period to the west—the city and nearby settlements began to lose population. By 1600 B.C.E., people appear to have abandoned their towns and moved north.

The researchers fed information from the soil samples, plus data from other sources such as Arabian Sea cores, into a climate model developed by Reid Bryson of the University of Wisconsin, Madison. The resulting curve for rainfall shows that for a millennium leading up to the Indus's peak, rainfall patterns—winter rains and the summer monsoon—remained remarkably stable. That changed dramatically in the same period that drought afflicted Mesopotamia.



Rain on the plain. During the height of the Indus civilization, the monsoon began to sputter (blue) while winter rains increased dramatically (red).

CREDITS (TOP TO BOTTOM): UNIVERSITY OF PENNSYLVANIA MUSEUM; REID BRYSON/UNIVERSITY OF WISCONSIN

"They went out of kilter," says Joseph Schuldenrein, who runs Geoarchaeology Research Associates, a Riverdale, New York–based consulting firm. Winter rains increased, but the monsoon became undependable—a pattern that continued for some 6 centuries. The result shows that the climate event did indeed affect the Indus region, says Weiss, although he has not yet seen the detailed data.

But the rainfall change did not spark a sudden collapse in Indus settlements, notes New York University archaeologist Rita Wright, who is part of the team. "As these changes occurred, it is clear that the Harappans were experimenting with new cropping patterns" to cope, for example by planting summer crops such as millet twice a season.

In the long run, however, their adaptation apparently failed, perhaps due to a lag time in the impact of the climate change, the researchers say. Vegetation and the landscape around the area's rivers slowly transformed, as plants vanished and rivers shifted course, according to geomorphological data the team gathered in the Harappa area. Those changes, rather than the change in rainfall per se, likely played a critical role in the move north, says Schuldenrein.

The Indus experience may hold a lesson for today. "Very large climatic changes can happen within a century," points out Bryson. And the success with which societies cope may depend on local impacts—and how adaptable the locals prove to be.

–ANDREW LAWLER

Diversity matters

984

Slowing deforestation

985

LETTERS

edited by Etta Kavanagh

When the Oil Supply Runs Out

THE ARTICLE "THE LOOMING OIL CRISIS COULD ARRIVE UNCOMFORTABLY SOON" (R. A. KERR, News of the Week, 20 Apr., p. 351) is far too equivocal in its discussion of such a vital topic, noting first that the most likely scenario is a resource-constrained peak by 2020, then that political factors must be taken into account in a discussion of peak oil production, and finally concluding that there is so much uncertainty that "predicting the peak may not be worthwhile."

Much, but not all, of the political uncertainty regarding production rates can be captured by partitioning conventional oil extraction into OPEC and non-OPEC components. This has been done by ExxonMobil and others (*1*–*4*); ExxonMobil has concluded that non-OPEC production will peak by 2010. On the basis of this forecast, ExxonMobil has publicly stated that it will build no new refineries, presumably because the crude supplies needed may not be available from OPEC producers. The high and rapidly fluctuating U.S. gasoline prices currently being experienced are due in large part to a shortage of domestic refinery capacity, so that we are in fact already feeling the effects of an imminent non-OPEC peak.

Recently, Ecuador rejoined OPEC, and Angola has also become a member. Over the next two or three years, it will become clear that crude oil is indeed a finite resource, and we will be forced to adapt to much higher petroleum prices as India and China continue to expand their automobile and airline fleets. Fortunately, there are many ways to cope with this new state of affairs, first and foremost by embracing energy efficiency and conservation not as virtues for the elite, but as urgent and universal national goals.

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Testosterone and Male Fertility in Red Deer

IN "MALE FERTILITY AND SEX RATIO AT BIRTH IN red deer" (Reports, 1 Dec. 2006, p. 1445), M. Gomendio *et al.* discovered that the proportion of males born to red deer was correlated with the degree of fertility of the fathers. These observations support the hypothesis that the strongly beneficial trait of male fertility favors the production of more sons that can then perpetuate this trait. This study provides insight into possible extragenetic contributions to sex ratios among offspring that likely have implications in other mammalian species, including humans.

The proportion of male births has been steadily declining in some human populations from North America and Europe (*1*). The reason for this decline is unknown, but the phenomenon has been associated with exposure to chemical pollutants (*2*–*5*). Among the Aamjiwnaang First Nation community (Ontario, Canada), not only is the proportion of male live births decreasing, but the magnitude of this disproportion has increased over time (*6*). Investigators have suggested that this localized disruption in sex ratio is a consequence of the abundant chemical industry in the vicinity (*6*).

A decrease in the proportion of male offspring has been associated with reduced testosterone levels or decreased testosterone/gonadotropin ratios in fathers (*7*, *8*). Gomendio *et al.* did not report testosterone levels among fathers in the studied red deer population. However, they associate fertility—the trait linked to altered sex ratio—with antler size. Testosterone is a major determinant of antler growth (*9*). Thus, it can be hypothesized that androgen status of fathers influences the proportion of males sired and that the decreasing proportion of male births documented in many human populations is due to declining testosterone levels among the fathers. A possible role for testosterone in regulating sex ratios of offspring has been debated for some time, but the issue remains unresolved. The study by Gomendio *et al.* provides new insight into a potential role for hormones in determining offspring sex in mammals, including humans.

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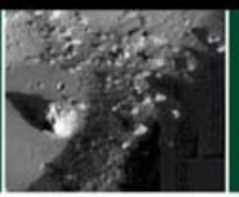
IN "MALE FERTILITY AND SEX RATIO AT BIRTH IN red deer" (Reports, 1 Dec. 2006, p. 1445), M. Gomendio *et al.* reported that in red deer, (i) male fertility is significantly and positively correlated with offspring sex ratio (OSR) (proportion of males), and (ii) the percentage of morphologically normal sperm correlates positively with OSR.

A decade of animal cloning
990



Gravel piles in space
993

These authors interpreted their results as supporting adaptive theory, but were uncertain of the identity of the proximate cause(s) of variation in OSR. They also noted that although much work has been done by adaptive theorists on OSRs of female mammals, little has been done by them on OSRs of male mammals. However, there are prodigious quantities of data relating the variation of men's OSRs to selected environmental factors. For instance, men's OSRs are affected by nine different adverse chemical exposures, five different pathological conditions, and four types of occupational exposure (*1*). In all 18 of these conditions, the OSRs correlated positively and significantly with men's testosterone concentrations. Indeed, there is strong evidence that the sexes of offspring of mammals (including humans) are partially controlled by the hormone levels of both parents around the time of conception (*2*, *3*). This would suggest that high levels of testosterone around the time of conception are associated with the subsequent births of sons.

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Response

WE REPORTED THAT MORE FERTILE RED DEER males, with a higher proportion of morphologically normal spermatozoa, produce a greater proportion of male offspring, who are likely to inherit enhanced fertility. Le Blanc and James suggest that testosterone may mediate the relationship between male fertility and offspring sex ratio (OSR) in this and other species, including humans. LeBlanc notes that, in our study population, male fertility is associated with antler size (*1*) and, on the basis of his premise that testosterone is a major determinant of antler growth, concludes that differences in OSR may be due to differences in testosterone levels between males. LeBlanc and James propose a role for testosterone by extrapolating from studies in humans where indirect evidence suggests that biases in OSR linked to environmental factors could be caused by changes in testosterone levels.

CREDIT: PHOTOS.COM

Although the idea has been around for some time, the hypothesis that testosterone influences OSR has not been properly tested. We do not have testosterone data from our OSR experiment, but we do have data on testosterone levels for a captive red deer population throughout the year ($N = 18$) and for a large sample of males from natural populations during the breeding season ($N = 77$), which we have used to test the relationships proposed.

Red deer are seasonal breeders and cast and regrow their antlers every year. In our captive population, testosterone levels remained low during antler growth, increased during antler mineralization, reached a peak just before the breeding season started, and decreased thereafter, similar to previous reports (*2*, *3*). Thus, although testosterone may control the timing of key events in the antler cycle, the observation that testosterone levels are low during antler growth supports the current view that the presumed positive link between testosterone levels and antler size is mistaken (*4*, *5*). In fact, the opposite may be true, at least in red deer, because males treated with anti-androgens grow larger antlers than controls, and testosterone reduces antler growth by influencing IGF-1 binding, the latter having an important role in antler growth (*5*).

Further evidence against the presumed link between testosterone levels and antler size comes from natural populations, where we found no relationship between males' testosterone levels during the breeding season and antler size. It should be noted that both variables are uncoupled in time, i.e., antlers grow in spring, when testosterone levels are minimal, and remain unchanged during the breeding season, when testosterone levels increase. Thus, the idea that testosterone levels during the breeding season are associated both with antler size and OSR would imply that males with higher testosterone levels during spring have increased antler growth rates, and that differences between males in testosterone levels remain consistent during the breeding season when absolute values increase. Further studies are needed to test these possibilities.

The annual cycle in testosterone levels is mirrored by changes in testes size, and, in natural populations, males with higher testosterone levels have larger testes and produce more sperm. However, the potential links between testosterone and other aspects of semen quality remain to be demonstrated.

The close relationship between testosterone and sperm production justifies the use of sperm numbers as an indirect measure of testosterone levels for each male. This allows us to test the presumed relationship between testosterone and OSR for the males used in our OSR experiment. In our study sample, there was no relationship between numbers of spermatozoa and OSR. Thus, it seems unlikely that differences in testosterone levels between males during the breeding season explain the biases in OSR observed.

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Further Notes on Quasi-Crystal Tilings

WE APPRECIATE THAT *SCIENCE* HAS CLARIFIED its news article ("Quasi-crystal conundrum opens a tiling can of worms," News of the Week, J. Bohannon, 23 Feb., p. 1066; see Corrections and Clarifications on page 982 in this issue) regarding our paper "Decagonal and quasi-crystalline tilings in medieval Islamic architecture" (Reports, 23 Feb., p. 1106). We certainly recognized that our study builds on earlier work, as acknowledged in our references (*3*–*6*, *14*, *18*–*19*), and citations therein, although more can be said. Many authors from Hankin in 1925 [(*14*) in our Report] to Wade

CORRECTIONS AND CLARIFICATIONS

News of the Week: "Quasi-crystal conundrum opens a tiling can of worms" by J. Bohannon (23 Feb., p. 1066). The article presented opinions of Dov Levine of the Israel Institute of Technology and Joshua Socolar of Duke University in a way that has led to misperceptions. The article discussed a paper by Peter Lu and Paul Steinhardt (*Science*, 23 Feb., p. 1106) on the use of tiling designs by medieval Islamic architects that form the basis of nonrepeating patterns called quasi-crystals. It went on to report that Levine and Socolar "doubt that the architects truly understood quasi-crystals." That comment—the only outside comment in the article on the paper's conclusions—is consistent with what was concluded in the Lu-Steinhardt paper itself; it does not, and was not meant to, contradict the central claim that the architects used a method capable of creating a perfect quasi-crystal tiling. The article also included a quote from Emil Makovicky of the University of Copenhagen that his earlier publication on Islamic tiling patterns was cited by Lu and Steinhardt "…in a way that [the ideas] look like their own." Immediately following, Levine and Socolar were quoted regarding Makovicky's contributions to the field. The context of their quotes implied that they agreed with Makovicky's characterization, but neither of them did so.

Special Section: Sustainability and Energy: Perspectives: "Biomass recalcitrance: engineering plants and enzymes for biofuels production" by M. E. Himmel *et al.* (9 Feb., p. 804): The legend describing panels B and C of Fig. 1 was reversed in the online version of the paper. Panel B shows the atomic force micrograph, and panel C shows the scanning electron micrograph. The legend was correct in print. The correct text was posted online on 13 February.

TECHNICAL COMMENT ABSTRACTS

Comment on "A Centrosome-Independent Role for γ-TuRC Proteins in the Spindle Assembly Checkpoint"

Stephen S. Taylor, Kevin G. Hardwick, Kenneth E. Sawin, Sue Biggins, Simonetta Piatti, Alexey Khodjakov, Conly L. Rieder, Edward D. Salmon, Andrea Musacchio

Müller *et al.* (Reports, 27 October 2006, p. 654) showed that inhibition of the γ-tubulin ring complex (γ-TuRC) activates the spindle assembly checkpoint (SAC), which led them to suggest that γ-TuRC proteins play molecular roles in SAC activation. Because γ-TuRC inhibition leads to pleiotropic spindle defects, which are well known to activate kinetochore-derived checkpoint signaling, we believe that this conclusion is premature.

Full text at www.sciencemag.org/cgi/content/full/316/5827/982b

Comment on "A Centrosome-Independent Role for γ-TuRC Proteins in the Spindle Assembly Checkpoint"

Beth A. A. Weaver and Don W. Cleveland

Müller *et al.* (Reports, 27 October 2006, p. 654) proposed a role for microtubule nucleation in mitotic checkpoint signaling. However, their observations of spindle defects and mitotic delay after depletion of γ-tubulin ring complex (γ-TuRC) components are fully consistent with activation of the established pathway of checkpoint signaling in response to incomplete or unstable interactions between kinetochores of mitotic chromosomes and spindle microtubule.

Full text at www.sciencemag.org/cgi/content/full/316/5827/982c

Response to Comments on "A Centrosome-Independent Role for γ-TuRC Proteins in the Spindle Assembly Checkpoint"

Hannah Müller, Marie-Laure Fogeron, Verena Lehmann, Hans Lehrach, Bodo M. H. Lange

Weaver and Cleveland and Taylor *et al.* contend that our data on the involvement of γ-tubulin ring complex (γ-TuRC) in the spindle assembly checkpoint (SAC) can be fully explained by kinetochore-derived checkpoint signaling. We maintain that (i) the interactions of γ-TuRC with Cdc20 and BubR1 and (ii) the activation of SAC by γ-TuRC depletion, in addition to the abrogation of kinetochore microtubule interactions, argue for a more complex mechanism of SAC signaling.

Full text at www.sciencemag.org/cgi/content/full/316/5827/982d

(*1*), Critchlow (*2*), and Kaplan (*3*) have related Islamic geometric patterns to configurations of polygons, including some with the same outlines as the decorated girih tiles introduced in our paper. Bonner [(*19*) in our Report] has applied these ideas to self-similar geometric patterns with five-fold and other symmetries. Makovicky [(*18*) in our Report], and previously Zaslavsky *et al.* (*4*) and Chorbachi [(*31*) in our Report], suggested relations between certain historic Islamic tilings and Penrose tilings based on studies of small isolated motifs or fragments embedded within manifestly periodic patterns.

We gladly acknowledge all these contributions, which complement our own. However, we wish to emphasize a few distinctions here. First, our approach was founded on the historical record, particularly the Topkapi scroll first understood and published by Gulru Necipoglu (Harvard University), who guided us. Insisting on exact reconstructions of historical monuments resulted in some differences from previous work; for example, our analysis of the Gunbad-i Kabud tomb tower (Figs. 2 and S6), based directly on archival photographs, differs systematically from the transcription used in reference (*18*) and reveals plainly the intentional periodicity and regular deviations from a true Penrose tiling. Second, our explanation of these patterns clearly differs from earlier ideas: We propose that historical designers constructed a wide range of patterns by tessellating with the same five units ("girih tiles") described in our paper, not merely polygons but shapes with specific interior line decorations that form the pattern when the tiles are joined together. Constructing patterns by laying these girih tiles edge to edge this way is simpler than other proposed methods; we have observed young children successfully applying it in the classroom. Moreover, other methods generate many patterns that do not appear historically; by contrast, we presented a series of patterns from historically significant buildings, scrolls, and Qurans throughout the medieval Islamic world that can all be constructed from the same five girih tiles (including their decorations). Third, our analysis of the Darb-i Imam shrine revealed two other novel elements—the explicit subdivision of these girih tiles into smaller girih tiles of the same shape, and a large fragment based on decagonal symmetry that is not embedded in a periodic matrix, properties sufficient to transform the Darb-i Imam shrine pattern into an infinite quasi-crystalline tiling. Our conclusions were guarded, concurring with the remarks by Socolar and Levine in the accompanying news article, suggesting that evidence beyond a single large fragment is needed to prove that the designers understood this possibility. We hope our small contribution, combined with the earlier works, will lead to further explorations of these impressive works of art and mathematics.

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

HISTORY OF SCIENCE

Science, the Fruit of Commerce

Jonathan I. Israel

Matters of Exchange is yet another reminder of the remarkable achievement of the Dutch during their Golden Age (roughly 1590 to 1713) and the centrality of their seaborne empire in the rise of modern Western commercial culture, financial organization, and the arts and sciences. If one puts it to academic colleagues working in other fields (including early modern Britain or America) that the Dutch Revolt and Golden Age were pivotal to the entire development of the modern West, they are quite likely to agree in very general terms. And yet this widespread assent in principle oddly fails to translate into much detailed study, outside the Netherlands, of the actual role of the Dutch in the sciences or anything more than the most ephemeral interest in the wider Dutch cultural context, thought, language, and literature. In nearly all the great American libraries—including Princeton and the New York Public Library, both situated on the territory of the former New Netherland (until 1664)—the collection of early modern Dutch books, and studies on them, remains quite disgracefully meager in quantity and quality.

Harold Cook (the director of the Wellcome Trust Centre for the History of Medicine at University College London) is the author of an impressive series of carefully researched studies focusing on the relationship in the 17th and 18th centuries between what he calls "the new philosophy" and medical science and between medicine and natural history. These include several articles on the influence of Far Eastern medicine on the West and others on such important figures as the philosopher and political economist Bernard Mandeville and the 18th century's leading medical authority, Herman Boerhaave. Cook's basic thesis in *Matters of Exchange* is that "the values inherent in the world of commerce were explicitly and self-consciously recognized to be at the root of the new science by contemporaries," that this was a correct perception, and that the Dutch being the most highly commercialized Western society in the 17th century was directly linked to the breadth, richness, and specific character of their contribution to the sciences.

The author is sensitive enough to recent reservations about the notion to refer to the "so-called scientific revolution" rather than to the Scientific Revolution with capital letters. Nevertheless, he clearly believes that there was a decisive breakthrough in Western science in the 17th century. He also holds that this development should be explained less in terms of a few great geniuses applying mathematics to astronomy and physics in new ways than by the acceleration of the movements and processes of world commerce "leading to countless efforts to find out matters of fact about natural things and to ascertaining whether that information was accurate and commensurable." The need for reliable information, new data, and solid facts, Cook argues, led to what he calls "this discovery of the world—its geography, peoples, plants and animals, and astrological and alchemical associations; the accumulation of specimens of it, the cataloging of its variety."

Matters of Exchange
Commerce, Medicine, and Science in the Dutch Golden Age

by Harold J. Cook

Yale University Press, New Haven, CT, 2007. 576 pp. $35. ISBN 9780300117967.

Especially admirable, it seems to me, are the several detailed chapters on the Western response to the information (geographical, medical, and botanical) gleaned from the Dutch East Indies, India, China, and Japan and the resulting work on the natural history of the Far East (most famously by "the Pliny of the Indies," Rumphius). Among the interesting people that appear in these chapters is the physician Jacobus Bontius, who spent four years at Batavia (i.e., Jakarta) before succumbing to disease in November 1631. During that short time, Bontius achieved the remarkable feat (given his strenuous duties) of gathering an unprecedented variety of scientific information, not least on tropical diseases (about which he learned much by conducting autopsies). Bontius summarized this aspect of his research in a Latin thesis written in 1629 that was eventually published under the title "On the proper treatment of diseases of the East Indies."

Cook strongly stresses the strictly empiricist character of medical and other scientific research conducted by the Dutch. A chapter titled "The Refusal to Speculate" includes, among much else, an excellent survey of the medical researches and theorizing of Boerhaave. In it, Cook rightly underlines Boerhaave's consistent advocacy, throughout his career, of starting with the observed facts and then only using natural reason to determine the meaning of these, without authorizing any search for first or ultimate causes. But

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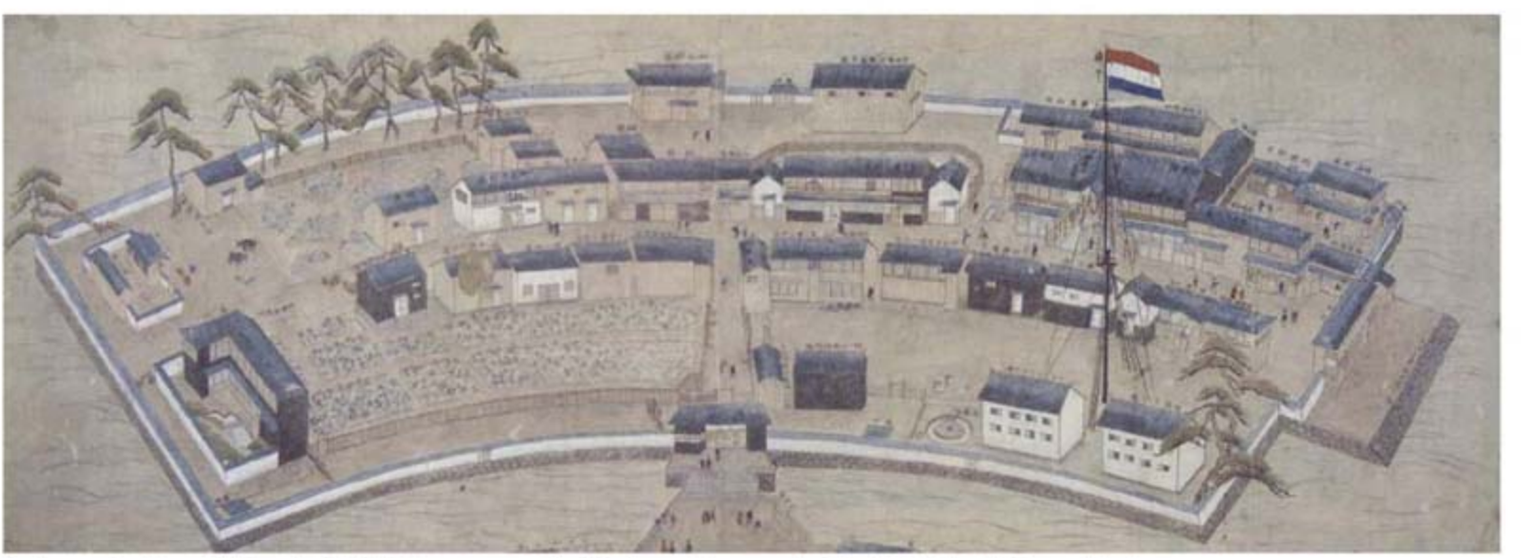

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Exchange site. From 1641 on, the Dutch in Japan were confined to the small man-made island of Deshima in Nagasaki harbor.

Cook's thesis about the empirical character of the scientific revolution goes beyond the statements made by earlier scholars. For he concludes that—even if most people preferred to "read" the 17th and 18th centuries as an age in which increasing knowledge and decreasing "superstition" resulted from the rise of "experimental science and philosophical enlightenment, with a growing material economy merely providing the means to sustain the lives of those who wished to devote themselves to advancing thought"—this revolution was not just coincidental in time with the development of the first global economy (by the Dutch and English) but also causally linked to that process. The new form of global commercial culture established by the Dutch more than any other Western nation emerges here as the key stimulus and shaping factor in generating the "so-called scientific revolution."

The inevitable implication of this argument is that the "new philosophy" and the advancing Enlightenment have been generally overrated as factors shaping the new culture of science, and religious factors have been as well. Perhaps Cook is right. But one does not need to be wholly convinced of his thesis to admire his achievement. *Matters of Exchange* is a book that will undoubtedly be fruitful, not least in stimulating fresh debate about the sources of the scientific revolution and the exact role of the strict empiricism so cherished by the Dutch and so famously theorized by Locke.

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PSYCHOLOGY

Diversity Paradoxes

Philip E. Tetlock

The Difference is brimming with so many intriguing insights and findings that I cannot do justice to them all. But this engaging book is also fated to be misinterpreted in so many different ways that I despair of preempting them all.

For analytical convenience, let's start by dividing the world into two types of people: those who divide the world into two types and those who do not. And let's suppose that this reviewer falls into the former group. I divide readers of Scott Page's book into two categories: cognitive egalitarians (who downplay standardized ability–test scores in college admissions and employment and who stress the need to include the previously excluded) and cognitive elitists (who have mirror-image priorities).

Valuing multiple perspectives. Sandra Dionisi's *Cubist Skyline*.

Casual readers could easily conclude that Page (a professor of economics and political science at the University of Michigan) has clinched the argument for the egalitarians. Indeed, Page arguably invites the interpretation that there may be no awkward efficiency-equality tradeoffs when he repeatedly declares that "diversity trumps ability." Careful readers will, however, heed the qualifications that Page attaches to his "diversity-trumps-ability" theorem—and the massive inferential gap between Page's elegant thought experiments and the messy real-world situations to which Page generalizes with varying degrees of caution.

Page focuses on two tasks, problem-solving and prediction, and relies on two explanatory concepts, perspectives and heuristics. Perspectives "are representations that encode objects, events, or situations so that each gets its own unique name." The more diverse the causal perspectives, the wider the range of potentially viable solutions a collection of problem-solvers can find. Heuristics are problem-solving tactics that tell problem-solvers working within a perspective how to search for potential improvements on solutions.

Page deploys computational models—populated with agents that interact in time and space according to computer-coded rules—to illustrate the power of diversity. The agents can represent virtually anything: from viruses to politicians.

Page's car-mileage thought experiment is representative of the challenges of moving from computer code to hypercharged real-world debates. Imagine a lot with 1000 cars. We want the car with the best gas mileage but only have data bearing on three perspectives on the causes of gas mileage: vehicle weight, height, and wheelbase. Solving the problem empirically—test driving each car—is prohibitively costly, so we must solve it heuristically. Page arrays the cars along each of the three causal-perspective axes and plots the mileage of each car tested. His program directs agents, each endowed with a particular one-dimensional perspective, to start their search with a randomly selected car and then move to the neighboring car. If that car has better mileage, the agent continues until reaching a local peak. If the second car gets worse mileage, the agent reverses direction and searches until reaching a local peak.

Imagine three such simple-minded agents working as a group. Each of their landscapes has local peaks, but a local peak on one dimension is rarely the local peak on the other dimensions. If the three agents cooperated, they could converge on a better solution faster and at less expense in effort. And, indeed, large populations of agents can—when aggregated—reliably reach solutions as good or better than those found by elite subsamples of the "smartest" agents.

In brief, diversity appears to trump ability—at least when we equate high ability with drawing lucky starting points in sharply constrained searches for solutions. But elitists will argue that the game was rigged. Would diversity still trump ability if we defined ability as capacity to scan all three dimensions simultaneously for peaks and spot promising starting points based on those scans (rather than randomly), or as capacity to see beyond one's immediate neighbors, or as capacity to resist premature closure and avoid confusing local optima with the global optimum? I suspect that the result would look more like the chess match between Kasparov and the 50,000 Internet challengers. The challengers did well, but they still lost. Moreover, we need to consider the cost of mobilizing 50,000 moderately to extremely skilled chess players to strategize almost as well as a grandmaster. The boundary conditions on diversity-trumps-ability may be longer—perhaps a lot longer—than Page acknowledges.

I conclude Page's pro-diversity argument applies to his own research program. If his agent-based models had been informed by a more diverse set of disciplinary perspectives (especially by work on expert systems and cognitive styles), he would have reached a more appropriately nuanced set of conclusions about the costs as well as the benefits of diversity. Ironically, therefore Page could be wrong in one respect because he is right in another. Readers should keep this paradox in mind before they export his research findings into messy policy debates over how much weight to give identity diversity in hiring university faculty—or, to switch perspectives, how much weight to give ideological diversity in hiring social scientists.

10.1126/science.1142673

The Difference
How the Power of Diversity Creates Better Groups, Firms, Schools, and Societies

by Scott E. Page

Princeton University Press, Princeton, NJ, 2007. 448 pp. $27.95, £17.95. ISBN 9780691128382.

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ENVIRONMENT

Tropical Forests and Climate Policy

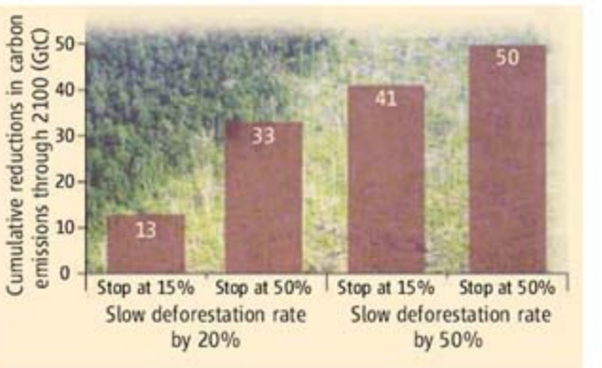
New science underscores the value of a climate policy initiative to reduce emissions from tropical deforestation.

Raymond E. Gullison,[1] Peter C. Frumhoff,[2]* Josep G. Canadell,[3] Christopher B. Field,[4] Daniel C. Nepstad,[5] Katharine Hayhoe,[6] Roni Avissar,[7] Lisa M. Curran,[8] Pierre Friedlingstein,[9] Chris D. Jones,[10] Carlos Nobre[11]

Tropical deforestation released ~1.5 billion metric tons of carbon (GtC) to the atmosphere annually throughout the 1990s, accounting for almost 20% of anthropogenic greenhouse gas emissions (*1*). Without implementation of effective policies and measures to slow deforestation, clearing of tropical forests will likely release an additional 87 to 130 GtC by 2100 (*2*), corresponding to the carbon release of more than a decade of global fossil fuel combustion at current rates. Drought-induced tree mortality, logging, and fire may double these emissions (*3*), and loss of carbon uptake (i.e., sink capacity) as forest area decreases may further amplify atmospheric CO_2 levels (*4*).

A combination of sovereignty and methodological concerns led climate policy-makers to exclude "avoided deforestation" projects from the 2008–12 first commitment period of the Kyoto Protocol's Clean Development Mechanism (CDM) (*5*). The United Nations Framework Convention on Climate Change (UNFCCC) recently launched a 2-year initiative (*6*) to assess technical and scientific issues and new "policy approaches and positive incentives" for Reducing Emissions from Deforestation (RED) in developing countries. This process was initiated at the request of several forest-rich developing nations, an indication of willingness to explore approaches to reduce deforestation that do not intrude upon national sovereignty. Recent technical progress in estimating and monitoring carbon emissions from deforestation (*7*) and diverse climate policy and financing proposals to help developing countries reduce their deforestation emissions (*8*) are currently being reviewed by the UNFCCC Subsidiary Body on Scientific and Technical Advice.

Whether a successful RED policy process can make an important contribution to global efforts to avoid dangerous climate change depends on two issues. First, are the potential carbon savings from slowing tropical deforestation sufficient to contribute substantially to overall emissions reductions? Second, is it likely that tropical forests (and the forest carbon) protected from deforestation will persist over coming decades and centuries in the face of some unavoidable climate change? The available evidence indicates that the answer to both questions is yes, especially in a future with aggressive efforts to limit atmospheric CO_2.



Estimated cumulative reductions in carbon emissions achievable by 2100 through reducing tropical deforestation. Calculations assume (i), deforestation rates observed in the 1990s decline linearly from 2010–50 by either 20 or 50%, and (ii) that deforestation stops altogether when either 15 or 50% of the area remains in each country that was originally forested in 2000 (*1*).

Potential savings for a range of deforestation levels are shown in the figure (above). Reducing deforestation rates 50% by 2050 and then maintaining them at this level until 2100 would avoid the direct release of up to 50 GtC this century (equivalent to nearly 6 years of recent annual fossil fuel emissions, and up to 12% of the total reductions that must be achieved from all sources through 2100 to be consistent with stabilizing atmospheric concentrations of CO_2 at 450 ppm (*1*) (figs. S1 to S5). Emissions reductions from reduced deforestation may be among the least-expensive mitigation options available (*9*). The IPCC estimates that reductions equal to or greater than the scale suggested here could be achieved at ≤U.S.$20 per ton CO_2 (*1, 10*).

Reducing deforestation not only avoids the release of the carbon stored in the conserved forests, but by reducing atmospheric carbon, it also helps to reduce the impacts of climate change on remaining forests. The experience of the 1997–98 El Niño Southern Oscillation Event (ENSO) demonstrates how climate change can interact with land-use change to put large areas of tropical forests and their carbon at risk. The extended dry conditions triggered by the ENSO across much of the Amazon and Southeast Asia increased tree mortality and forest flammability, particularly in logged or fragmented forests. Globally, increased forest fires during the 1997–98 ENSO released an extra 2.1 ± 0.8 GtC to the atmosphere (*11*).

Even in non-ENSO years, global warming may be putting tropical forest regions at risk of more frequent and severe droughts. Over the last 5 years, a number of Amazon Basin and Southeast Asian droughts have been uncoupled from ENSO events but have coincided with some of the warmest global average temperatures on record.

In recent decades, carbon losses from tropical deforestation have been partly or largely offset by a tropical sink (*12*). Forest sinks are, however, unlikely to continue indefinitely, and continued warming will likely diminish and potentially even override any fertilization effects of increasing CO_2. Climate change might also adversely impact tropical forests by reducing precipitation and evapotranspiration, making them drier, more susceptible to fires, and more prone to replacement by shrublands, grasslands, or savanna ecosystems (*13*), which store much less carbon. In the Amazon Basin, continued deforestation may disrupt forest water cycling, amplifying the negative impacts of climate change (*1*).

A new generation of coupled climate-carbon models is being used to explore the prospects for the persistence of tropical forests in a changing climate. A widely discussed early

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study projected that business-as-usual increases in CO_2 and temperature could lead to dramatic dieback and carbon release from Amazon forests (*14*), raising concerns that high sensitivity of tropical forests to climate change might compromise the long-term value of reduced deforestation, with dieback releasing much of the carbon originally conserved. However, of 11 coupled climate-carbon cycle models using the IPCC's mid-to-high range A2 emissions scenario, 10 project that tropical forests continue to act as carbon sinks, albeit declining sinks, throughout the century (fig. S6). The moderate sensitivity indicated by the new results suggests that reducing deforestation can result in long-term carbon storage, even with substantial climate change. Aggressive efforts to reduce industrial and deforestation emissions would likely further reduce the rate of decline and risk of reversal of the tropical sink (*1*) (fig. S6).

While no single climate policy approach is likely to address the diverse national circumstances faced by forest-rich developing countries seeking to reduce their emissions, there are promising examples of countries with adequate resources and political will that have been able to reduce forest clearing (*10*, *15*). In some countries, it may be possible at relatively low cost to reduce emissions from deforestation and forest degradation that provide little or no benefit to local and regional economies. For example, reducing accidental fire and eliminating forest clearing on lands that are inappropriate for agriculture are two promising low-cost options for reducing greenhouse gas emissions in Brazil and Indonesia.

Most deforestation for cattle production in Amazonia yields unproductive pasture but releases hundreds of tons of CO_2 per hectare. Compensating landowners to keep their land in forests instead of creating pastures could be done at relatively low carbon prices (*16*).

Other measures are unlikely to be implemented at large scales without financial incentives that may be feasible only within the framework of comprehensive environmental service payments, such as through carbon-market financing (*16*, *17*). In forests slated for timber production, for example, moderate carbon prices could support widespread adoption of sustainable forestry practices that both directly reduce emissions and reduce the vulnerability of logged forests to further emissions from fire and drought exacerbated by global warming. On forested lands threatened by agricultural expansion, financing could provide significant incentives for forest retention and enable, for example, more effective implementation of land-use regulations on private property and protected area networks (*18*).

Parties to the UNFCCC should consider adopting a range of options, from capacity building supported by traditional development assistance to carbon-market financing to help developing countries meet voluntary national commitments for reductions in forest-sector emissions below historic baselines (*7*). Voluntary commitments, which were put forward by several tropical forest nations (*19*), would substantially address a concern associated with the project-based approach of the CDM that emissions reductions from a site-specific project might simply be offset by increased deforestation elsewhere (*10*).

Key requirements for effective carbon-market approaches to reduce tropical deforestation include strengthened technical and institutional capacity in many developing countries, agreement on a robust system for measuring and monitoring emissions reductions, and commitments to deeper reductions by industrialized countries to create demand for RED carbon credits and to ensure that these reductions are not simply traded off against less emission reductions from fossil fuels.

Beyond protecting the climate, reducing tropical deforestation has the potential to eliminate many negative impacts that may compromise the ability of tropical countries to develop sustainably, including reduction in rainfall, loss of biodiversity, degraded human health from biomass burning pollution, and the unintentional loss of productive forests (*16*). Providing economic incentives for the maintenance of forest cover can help tropical countries avoid these negative impacts and meet development goals, while also complementing aggressive efforts to reduce fossil fuel emissions. Industrialized and developing countries urgently need to support the RED policy process and develop effective and equitable compensation schemes to help tropical countries protect their forests, reducing the risk of dangerous climate change and protecting the many other goods and services that these forests contribute to sustainable development.

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1. Further information can be found in supporting material on *Science* Online.
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Supporting Online Material

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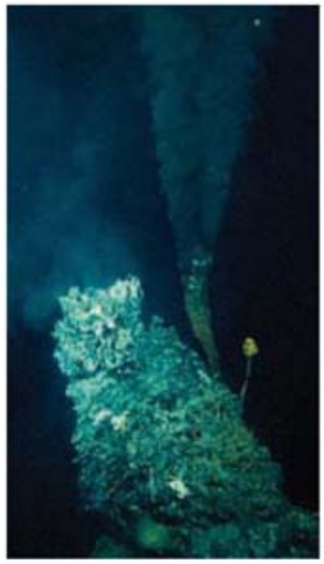
ECOLOGY

Danger of Deep-Sea Mining

Plans for deep-sea mining could pose a serious threat to marine ecosystems.

Jochen Halfar[1] and Rodney M. Fujita[2]

Over the past few months, the possibility of mineral exploitation in the deep sea (*1*) has moved closer to reality with completion of the first undersea exploration for massive sulfide deposits. Analyses of target deposits in a zone of active hydrothermal vent systems in the territorial waters of Papua New Guinea (PNG) have revealed gold, copper, zinc, and silver in concentrations that far surpass those of current terrestrial mining ventures (*2*). With mining technology in an advanced stage of development, skyrocketing metal prices, and depletion of metal-rich terrestrial mines, sea-floor mining activities are now scheduled to begin by 2009.



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Initial interest in deep-sea mining was centered on extracting manganese nodules from spatially extensive sea-floor deposits in international seas distant from continents. However, ratification of the United Nations Convention on the Law of the Sea in 1994, which imposed financial burdens and environmental safeguards, together with low metal prices, drastically lowered interest in nodule mining. Prospecting and exploration activities have since shifted to the Exclusive Economic Zones (EEZs), where it is the responsibility of individual nations to issue mining licenses and define environmental safeguards. Discovery of extensive massive sulfide deposits at commercial ore grades within the EEZs of PNG and, more recently, New Zealand has set off a new phase of exploration (*3*).

The first site for such mining is expected to be the Manus backarc basin of PNG, in close proximity to active sulfide-forming hydrothermal vent systems. Hydrothermal vents are home to unique and diverse ecosystems (*4*). They are not only of scientific interest, but are being explored for pharmaceutical and biotechnological applications (*56*). Whereas individual manganese nodule mine claims extend across sea floor areas the size of Switzerland, massive sulfide mining will concentrate on small (1 km^2 in size), high-grade deposits within the uppermost 20 m of the sea floor. An average of 2 megatons of ore per year is to be extracted by Nautilus Minerals, Inc., in a single strip-mining operation using remotely operated underwater mine cutters. It will be transferred from the sea floor to a mining platform by hydraulic pumps (*6*).

Environmental risks including benthic disturbances, sediment plumes, and toxic effects on the water column have been assessed for the large manganese nodule mining endeavors in the equatorial Pacific (*7*). These risks were judged to be so large and unpredictable that a number of studies recommended the abandonment of manganese mining efforts to avoid a large-scale and long-term risk to Pacific ecosystems and fisheries (*8*). Benthic disturbances and far-reaching sediment plumes would probably be less during massive sulfide mining (relative to nodule mining) because of the absence of sediment cover on the recently created ocean floor of active hydrothermal vent systems. However, explored mining sites are less than 1 km from active vents, where there is a likely potential of smothering, clogging, and contamination of vent communities by drifting particles.

Organisms surviving these perturbations would be subject to a radical change in habitat conditions with hard substrata being replaced by soft particles settling from the mining plume (*5*). Mining could also potentially alter hydrologic patterns that supply vent communities with essential nutrients and hot water. A further problem may arise during dewatering of ores on mining platforms, resulting in discharge of highly nutrient enriched deep-water into oligotrophic surface waters, which can drift to nearby shelf areas.

These impacts may not be limited to ecosystems within the EEZ of the country issuing mining permits and could thus be in violation of international environmental law (*9*). If the first deep-sea mining effort is successful, a wave of interest in deep-sea mining of massive sulfide deposits is likely to result. In fact, 250 of these deposits have been identified in deep-sea areas worldwide (*10*).

There has been little progress toward creation of environmental regulatory systems specific to deep-sea mining by governments with jurisdiction over massive sulfide deposits. Some of these governments have a poor track record of mine oversight and regulation on land, so prospects appear poor for sound regulation of underwater mining (*11*, *12*). It is time to implement scientific, technological, and legal measures to minimize negative environmental impacts (including discouraging deep-sea mining activities near sensitive habitats) and to set up mechanisms to recover costs of regulation and enforcement from this nascent industry. Large capital investments and generation of revenues by underwater mining operations are likely to make regulation after onset of commercial operations even more difficult once deep-sea mining becomes a reality.

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10.1126/science.1138289

CANCER

Converging on β-Catenin in Wilms Tumor

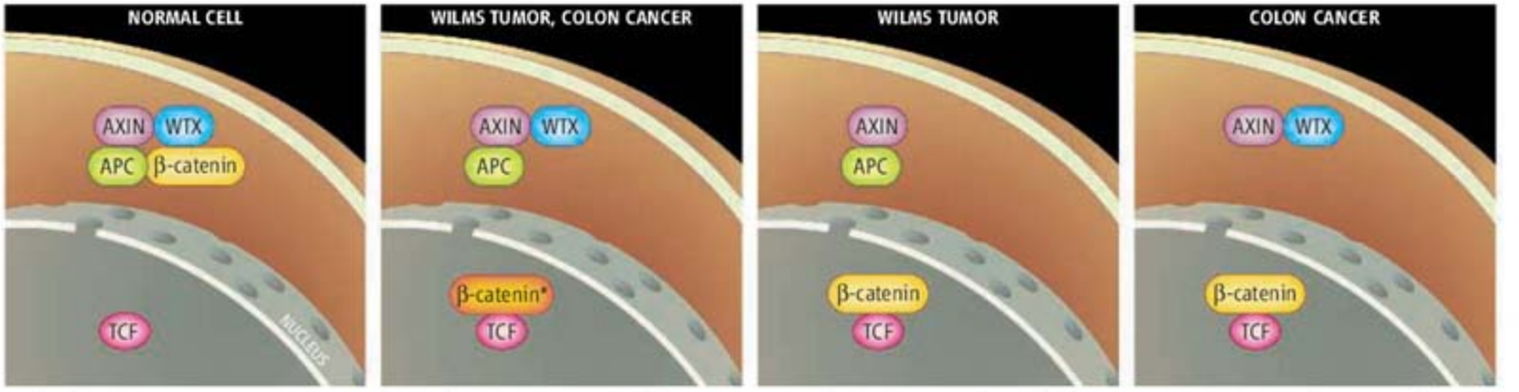
A common thread in some cancers is mutations in a developmental signaling pathway that ultimately affect the action of a single component.

Roel Nusse

Wilms tumor is a cancer of the kidney, occurring mostly in children and sometimes running in families (*1*). Genetic alterations in these tumors include mutations in the protein β-catenin (*2*), a component of a signaling pathway controlled by the secreted morphogen WNT. WNT–β-catenin signaling is particularly important during animal development. A subset of these tumors not only has mutations in the gene encoding β-catenin, but also lacks a normal tumor-suppressor gene, *WT1*. There are, however, many cases of Wilms tumors without mutations in either gene. A recent paper in *Science* reported another tumor-suppressor gene in Wilms tumor, *WTX* (*3*). On page 1043 in this issue (*4*), Major *et al*. show that WTX operates through β-catenin, down-regulating its activity. Wilms tumor thereby joins a growing number of human cancers caused by β-catenin activation.

The story of WTX is a convergence of two independent lines of research. Rivera and colleagues (*3*) used a high-resolution screen to detect alterations in DNA copy number in Wilms tumor, identifying deletions in a gene on the X chromosome called *WTX*. This gene is inactivated in about one-third of Wilms tumors, at the somatic-cell level. Remarkably, *WTX* is inactivated by a monoallelic "single-hit" mutational event. This mode of oncogenesis differs from the inactivation of most tumor-suppressor genes, which are biallelic—that is, one allele is inactivated in the germ line, followed by mutation of the second allele at the somatic-cell level. A single hit can have phenotypic consequences if the gene is located on the X chromosome (X-linked), and indeed, *WTX* mutations are found on the single X chromosome in tumors from males and the active X chromosome in tumors from females. Tumors with mutations in *WTX* do not have *WT1* mutations. This pattern of exclusive mutations is interesting, because it may indicate separate pathways leading to a similar end point in causing cancers. So what would this end point be?

An early clue came from observations that many Wilms tumors with mutations in *WT1* also either have sustained activating mutations in the β-catenin–encoding gene or have β-catenin protein present in the nucleus of tumor cells (*5*). Both observations indicate that the WNT signaling pathway is activated (*6*) because the nuclear translocation and activity of β-catenin are key events in WNT signaling. In normal cells, β-catenin is destroyed in the cell's cytoplasm by a complex of proteins that include AXIN and adenomatous polyposis coli (APC) (see the figure). This keeps β-catenin expression levels low, because as a consequence of associating with the AXIN-APC complex, β-catenin becomes amended with ubiquitin molecules and thus, targeted for degradation by the proteasome (*7*, *8*). After WNT binds to its receptor at the cell surface, β-catenin is no longer degraded, accumulates in the cytoplasm, and eventually moves to the nucleus, where it partners with the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors to control gene expression. Several components of the WNT signaling pathway have already been implicated in human tumors or experimental cancer models, particularly APC, which was first isolated as a tumor-suppressor in human colon cancer. In addition, activating mutations in the human gene encoding β-catenin have been found in human colon cancer and melanomas, and Wilms tumor.



Variations en route to cancer. In normal cells, β-catenin is controlled by interactions with APC, AXIN, and WTX (**left**). Activating mutations in β-catenin (shown by an asterisk) can drive the protein to the nucleus, where it activates transcription together with the transcription factor TCF (**middle**, **left**). In Wilms tumor (**middle**, **right**), loss of WTX function results in translocation of β-catenin to the nucleus, whereas loss of APC function leads to colon cancer (**right**).

Working from the perspective of WNT signaling, Major *et al*. show that WTX is a new component of the protein complex that sequesters β-catenin in the cytoplasm and blocks its gene-regulatory activity. They used a proteomics approach: "fishing" for a binding partner of β-catenin in cell lysates by tandem-affinity protein purification and mass spectrometry (*4*). Such experiments are powerful but potentially problematic because of spurious protein interactions. However, because β-catenin is in a complex with AXIN and APC, these known binding partners can both serve as an internal control for the screen and as fishing "baits" in their own rights. Through these reiterative searches, WTX turned up as a partner for many known components in the β-catenin–AXIN–APC complex. WTX fulfills all the criteria of being yet another negative regulator of β-catenin: Overexpression of WTX reduces WNT–β-catenin signaling, whereas inhibiting WTX enhances β-catenin activity in

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the nucleus, both in cultured cells and in animals. The exciting conclusion is that *WTX* is a tumor-suppressor gene in Wilms tumors because its normal function is to control β-catenin activity.

These findings are revealing for a number of reasons. Apart from Wilms tumor, footprints of β-catenin activity have been detected in other human cancers, mostly by virtue of the nuclear presence of the β-catenin protein. In many of those cases, there has been no evidence that the known components of the WNT signaling pathway are mutated, suggesting that β-catenin becomes activated without any genetic alterations. But the new knowledge provided by Major *et al.* invites speculation that *WTX* is in fact mutated in these cancers.

In the absence of data on the possible involvement of *WTX* in other cancers, we may also speculate about the tissue specificity of tumor-suppressor genes. Clearly, Wilms tumors can be caused by activating mutations in the gene encoding β-catenin or by loss-of-function mutations in *WTX*. Other cancers, particularly colon cancer, may result from similar activating mutations in the β-catenin–encoding gene, but the major tumor-suppressor gene mutated in colon cancer is *APC*. Why this specificity? Are *WTX* and *APC* functionally redundant, meaning that loss of one will not lead to β-catenin activation, unless the other gene is not expressed? This possibility invites careful examination of the expression of *WTX* and *APC* in normal cells before they become cancerous. An X-linked tumor-suppressor gene is a time bomb waiting to go off, so there must be mechanisms to protect cells against loss of *WTX*. Such mechanisms could include *WTX* homologs on autosomes, perhaps expressed in cells other than kidney cells.

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10.1126/science.1143337

PHYSICS

Condensates Made of Light

At low temperature, atom wave functions can lock together. Such a state has now been seen in trapped photons and electron-hole pairs.

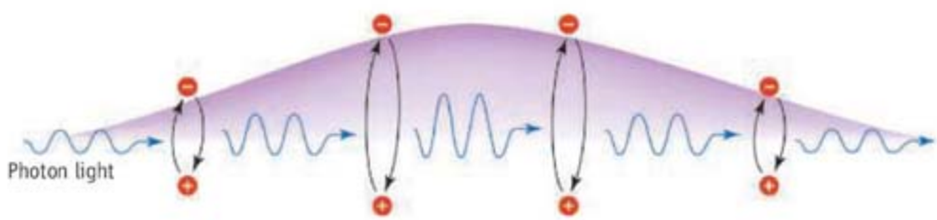
Peter Littlewood

A Bose-Einstein condensate (BEC) is the remarkable state of matter obtained when the collective quantum mechanical desire of atom waves to synchronize defeats their random motion in a normal liquid. Predicted by Einstein in 1924 and first observed with the discovery of superfluid helium in 1937, BEC has been subjected to intense study in the past decade, facilitated by the development of experimental methods of trapping and cooling of atomic gases at microkelvin temperatures. On page 1007 of this issue, Balili *et al.* (*1*) demonstrate trapping of a different kind of "atom" that can condense in the relative warmth of tens of kelvin, or perhaps even higher. By creating these warmer condensates, the researchers have now greatly expanded the variety of systems in which quantum coherence can be studied. Apart from the substantial fundamental interest in quantum coherence, such systems might become the building blocks of future quantum information processing systems.

BEC is a quantum phenomenon that depends on the overlap of atomic wave functions. An atom has a wave function whose size depends inversely on the atomic mass; hence, to reach BEC for massive atoms in a dilute gas, the temperature must be reduced below 1 μK, and even for dense liquid ^{4}He the transition temperature is only 2 K. But if it were possible to make a high-density gas of "atoms" whose mass is small, then quantum coherence might be expected to occur at much higher temperatures. Using a special kind of very light atom called a polariton—whose mass is as small as 0.0001 of the mass of an electron—several groups have been making progress toward this goal.

The trick to making a very light atom begins with the observation that the absorption of a photon by a semiconductor creates an electron in an excited state while leaving behind a positively charged "hole" (see the figure). This electron-hole pair can be bound into an atomic state, just like the proton and electron of the hydrogen atom, but the mass of the new particle—called an exciton—is much smaller. Of course such an "atom" is transient—it will vanish by reradiating a photon—but now one can play a second trick by placing mirrors on the sample. Then the photon bounces back and forth. If treated classically, it would be reabsorbed (by forming excitons) and re-emitted many times (by recombining excitons) before eventually escaping. In a quantum system, the superposition of the exciton and photon leads to the formation of yet another particle, which is known as a polariton. Because the photon is massless, polaritons are extremely light relative to the atoms typically found in BEC, and hence they offer the basis for exciting new quantum physics.

High-quality mirrors are difficult to make, but trapped "microcavity" polaritons were first made by semiconductor engineering in the early 1990s (*2*, *3*). Progress in making dense polariton gases inside these microcavities has been rapid in recent years but has usually occurred under nonequilibrium conditions. The challenges include cooling particles whose lifetime (from leaking through the mirrors) is measured in picoseconds, and making traps in which the particles can



Lightweight "atom." Photons from a laser (blue arrows) excite electron-hole pairs called excitons (black arrows). The excitons and photons form a quantum state called a polariton with a mass much less than that of an electron. Balili *et al.* have now trapped a quantum condensate of polaritons.

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equilibrate before the polaritons escape from the cavity as a puff of photons.

Last year, Kasprzak *et al.* (*4*) produced good evidence for an equilibrated BEC of polaritons, although in an open system without a trap to confine them. The energy level of an exciton can be shifted a little by squeezing the sample, which allows the exciton and photon to be tuned in or out of resonance, thereby weakening or strengthening polariton binding. Balili *et al.* have cleverly used a sharp pin to make an inhomogeneous strain, producing a system close in spirit to that of trapped atomic gases. Moreover, their host system is the widely used III-V semiconductor alloy GaAs rather than the less tractable and more disordered CdTe used by Kasprzak *et al.* This will open the field to a wider community.

Aside from the higher temperatures for the onset of coherence, there are a number of special differences from the atomic systems that give additional richness [see (*5*) for a review]. The current systems are inherently two-dimensional, so that the BEC phase transition in equilibrium should be of a special variety known as a Berezhinskii-Kosterlitz-Thouless transition, where spatial correlations of the coherence have a finite range giving a predicted experimental signature of the emitted photons. The polaritonic atoms are large—roughly the scale of the wavelength of light, about 1 μm—and thus overlap at very low density, quite unlike the dilute atomic gases whose interactions are short-range. And because the mirrors are not perfect, the polaritons escape (to be emitted as photons) and the trap must be continuously repopulated, which adds a continuous perturbation to the macroscopic coherence.

The light emitted from the condensate is, of course, as nearly coherent as a two-dimensional system can be—this being one of the tests of condensation—which makes the whole device behave like a special kind of (low-threshold) laser. And the output coupling to coherent light was already demonstrated some time ago by experiments that showed that resonant laser coupling could drive condensate formation through nonlinear scattering (*6*). There is thus a lot to explore.

Current experiments, although warm with respect to ultracold atoms, are still at cryogenic temperatures. The ultimate transition temperature is set by the exciton-photon coupling, measured by an energy scale known as the Rabi splitting. This is limited by fundamental properties of the material and device structure; its value is 13 meV (~150 K) in the GaAs system and about twice that in CdTe. In microcavities containing some organic molecules, Rabi splittings as large as 80 meV have been seen (*7*)—which is tantalizing for a room-temperature device. These objects are, on the one hand, a new kind of low-threshold laser, but the fact that they consist of coherent quantum objects (unlike a regular laser) puts them potentially in the class of quantum devices. A rash speculation is that a small polariton condensate could become the basis for an elementary quantum computer, but the easy coupling to light might simplify the wiring issues that many quantum information technologies find challenging.

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DEVELOPMENTAL BIOLOGY

A Decade of Cloning Mystique

Was Dolly a fluke or one of the biggest breakthroughs in modern science? Probably both.

Jose Cibelli

Ten years ago, Ian Wilmut, Keith Campbell, and their colleagues from the Roslin Institute in Scotland announced the first cloned adult mammal—a sheep named Dolly—using a technique called somatic cell nuclear transfer (*1*). Since then, the experiment has been independently replicated in 16 other mammalian species. Laboratories around the world launched efforts to identify the mechanism responsible for this phenomenon. Hundreds of peer-reviewed manuscripts later, we are left with many unanswered questions about the technique and are still unable to substantially increase its efficiency. For all species cloned by this method, less than 10% of embryos transferred into the uterus will produce a healthy clone. Why?

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Wilmut and Campbell's curiosity radically changed our views on the plasticity of the genome. The technique, in which the nucleus of an animal's somatic cell is inserted into an enucleated, unfertilized egg cell (called an oocyte) of the same species, essentially takes a differentiated cell and "turns it back," in a developmental sense, to a zygote, poised to develop into a fetus and mature adult that is genetically identical to the animal that provided the somatic cell nucleus. The old dogma that a differentiated cell can never turn back in development has been replaced by a new one stating that somatic cell nuclear transfer is possible and that our failures are attributable to insufficient understanding of the mechanisms that govern how a somatic cell nucleus is reprogrammed by the cytoplasm of an oocyte.

When performing somatic cell nuclear transfer, we are asking a somatic cell to turn into a gamete in a matter of hours, a process that normally takes months (*2*). Shortly thereafter, we expect such a pseudo-gamete to "turn into a fertilized egg," or zygote (coaxed by electrical or chemical stimulation in vitro), ready to divide and form an embryo. This is a tremendous undertaking for a genome that the day before was governing the identity and physiology of a completely different cell type. Now we are faced with trying to improve a technique that supports a process that is clearly unnatural. Should we? We cannot afford not to. Beyond the obvious practical benefits we might expect from achieving success—such as agricultural cloning (livestock production) and therapeutic cloning (generating stem cell–derived cell lines for understanding devastating diseases)—it poses a scientific challenge that goes to the heart of developmental biology.

Ten years have not been enough time, though; the long list of unanswered questions about animal cloning reflects how our understanding is stalled at a fundamental level. For instance, is somatic cell dedifferentiation or embryonic differentiation the step at which

the process stumbles? Can we render a nucleus more susceptible to the reprogramming action of the egg? How much responsibility for the outcome should either constituent be given? Can we reprogram a primate somatic cell? Why do cells, isolated at the same time from the same tissue of a given individual, have different cloning efficiencies? And the most important question: What is the gene(s) whose expression in the egg is critical for reprogramming a somatic nucleus?

Still, not all is uncertain; some progress has been made. We know that nuclei from highly differentiated cells can be reprogrammed. Despite suggestions that Dolly was cloned from a less differentiated cell fortuitously picked from among differentiated mammary gland cells, doubts were put to rest with the birth of mice cloned from mature lymphocytes and olfactory neurons. Clearly, almost any terminally differentiated cell can be forced to reenter the cell division cycle, proliferate, and form a new individual (*3*–*5*).

We also realize now that aberrant gene expression in cloned embryos can happen any time and in any cell. There is a failure to either shut down or reactivate genes in a timely manner. Candidate-gene expression studies among different mammalian species and laboratories have shown a wide array of gene deregulation. This also applies to imprinted genes (*6*). For cloned embryos transferred to the uterus, abnormal gene expression in the trophoblast cells of an early embryo (blastocyst) can translate into failure to form a normal placenta, claiming the life of the clone and sometimes, its surrogate mother (*7*).

Early on, we thought that animals cloned from an adult would display the biological age of the founder (the donor of the nucleus). This stemmed in part from analyzing the length of Dolly's telomeres (regions at the ends of chromosomes involved in DNA stability), which were apparently shorter than the founder's (*8*). Every time an adult somatic cell divides, its telomeres get shorter. This has been associated with aging and age-related diseases (*9*). But subsequent work has shown that in certain cloned animals, telomere length was not only restored but in some instances extended beyond that of the founder (*10*–*12*). Thus, for the first time, we have found a situation where the telomeres of a somatic cell can be extended without having been transformed into a tumor cell.

Epigenetic modification of DNA that alters gene expression is a normal process that still occurs in embryos derived from somatic cell nuclear transfer. These chemical-based alterations, which do not happen all at once, occur soon after embryogenesis begins, and continue during development before the embryo is implanted in the uterus, and even afterward. We know that cloned embryos can benefit from a culture medium that supports somatic cell survival during the initial cycles of embryonic cell division (*13*). This is likely due to a delay in switching from somatic to embryonic cell "mode." It remains to be determined whether this apparently abnormal epigenetic reprogramming is compatible with normal embryonic development after implantation. Perhaps the rare embryo that develops into a healthy offspring has its own pattern of gene expression, different from that of an embryo that arises from normal fertilization.

Soon after the nucleus of a somatic cell is delivered into the oocyte, chromatin (the DNA and protein constituents of chromosomes) begins a remodeling process whereby dynamic structural changes control the expression of genes. We've discovered that these changes recapitulate those occurring after normal fertilization. Histone methylation and acetylation, and DNA methylation occur in a manner similar to that in a fertilized embryo. However, the enzymes that catalyze the chromatin-remodeling processes fail to do so for reasons yet to be explained.

We have seen some cloned animals that are phenotypically normal. Nonetheless, a large proportion of cloned fetuses die in utero, and some are also born with malformations. But for most species cloned so far, a subset of clones show normal physiological parameters and are currently aging normally. And, although the percentage of normal animals born from cloned embryos is extremely small, it underscores the fact that this manmade procedure can sometimes, albeit randomly, work.

Are we closer today to finding the mechanism(s) responsible for somatic cell nuclear transfer? Yes, but not by much. We've spent the last decade focused on experiments that were goal directed. We either replicated the procedure in different species or worked on experiments that, while important, were designed to test how far we can go with this technique. Enough has been done on that front. Now the challenge to understand mechanisms must be tackled. A dearth exists in the current literature of functional approaches to understand the process. Several candidate genes have surfaced that make good targets for experiments on loss and gain of function. Furthermore, conservation of the core cellular reprogramming

Ten years of clones. (**Top** to **bottom**) Wolf, muflon, African wild cat, dog, sheep, mule, domestic cat, buffalo, mouse, goat, rabbit, horse, gaur, cow, pig, rat, ferret.

CREDITS: WOLF, DOG, SHEEP, MULE, GOAT, RABBIT, PIG/PHOTOS.COM; MUFLON, PETRA KARSTEDT, AFRICAN WILD CAT/SONELLE/JOHANNESBUG ZOO, SOUTH AFRICA; RAT, JANET STEPHENS; MOUSE/RASBAK; CAT, DAVID DE LOSSEY/GETTY; BUFFALO, ANUP SHAH/GETTY; HORSE, BILL TARPENNING/USDA; GAUR, COLINT; COW/PHOTODISC; FERRET, TERRY WHITAKER/FRANK LANE PICTURE AGENCY/CORBIS

mechanism seems robust; this can facilitate comparative genomic and proteomic studies among species.

Finding the gene(s) responsible for reprogramming will mark a crucial turning point for this technique in the next decade of animal-cloning research. We need to devise more rational experiments that can move the efficiency of somatic cell nuclear transfer closer to that obtained by in vitro fertilization, a welcome improvement for those interested in agricultural and pharmaceutical applications. Unveiling the genes and pathways involved in the cloning procedure is the first step to creating reasonable approaches for generating human cells that can later be used in therapy. Only then will so-called (and still hypothetical) therapeutic cloning become obsolete.

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10.1126/science.1143512

OCEAN SCIENCE

Highly Active Eddies

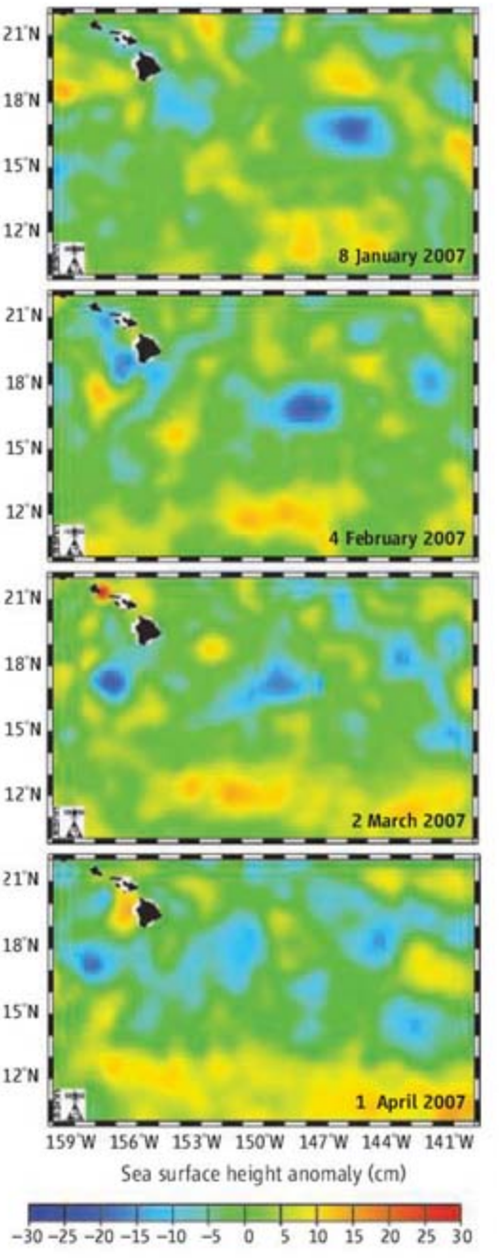
Anthony F. Michaels

The observation that biological activity in eddies can be very high may help explain why measurements of ocean productivity have varied widely.

The oceans, long a source of mystery in science, literature, and exploration, still hold many secrets. How we understand the ocean often depends on the tools used, the time scales of observation, and the internal traditions in subsets of this interdisciplinary field. One long-standing conundrum in ocean biogeochemistry has been the contrast between estimates of basic ocean properties when made at local scales versus estimates that average over whole ocean basins. Two papers in this issue report important advances toward resolving these differences (*1*, *2*).

For many important and interconnected biogeochemical rates—such as the rates of biological productivity at the surface, the rate at which organic matter sinks out of the surface layer, respiration and remineralization in the deep sea, and the mixing of nutrients back to the surface—estimates that should, in theory, all agree have differed by as much as an order of magnitude (*1*–*3*). Generally, local measurements give rates that are much lower than estimates that average over very large time and space scales. Mesoscale eddies—swirls in the ocean on scales of 50 to 200 km—are often invoked to explain the discrepancies. The direct measurements of ocean eddies reported in this issue (*1*, *2*) provide crucial support for this idea.

Ocean science has an unintended tradition of undersampling. At each local site, the phytoplankton productivity or amount of sinking organic matter can be directly measured for that location on that day. The oceans are enormous. Ships venture slowly across the sea, stopping occasionally to lower instruments on wires or to collect liters of water for analysis. Over time, the number of discrete measurements has increased slowly, yet the amounts of water that are actually sampled are even less than the proverbial drop in the bucket. Some scientists have therefore searched for ways to measure ocean properties that are inherently averaged over large areas and long time scales. By measuring properties like the concentration of oxygen in the deep sea, coupled to sophisticated estimates of the time since that water last equilibrated with the atmosphere, researchers can create an integrated estimate of the overall level of biogeochemical activity in the basin. These integrated approaches usually yield much higher rates of biological activity than those seen by biologists making direct measurements in the surface ocean. The conundrum could stem from two sources: The measurements themselves could be inaccurate, or the local approaches may not resolve all of the natural variability, missing some very active periods or places. Initially, scientists focused mostly on the measurement techniques for primary production and sinking particles. Trace-metal contamination seems to have resulted in artificially lower estimates of primary production. Sediment traps seem to be sensitive to hydrodynamics, the capture of swimming animals, and dissolution of the particles. Improved methods have helped to close part of the gap (*4*, *5*).



Tracking the eddies. In this series of images of sea surface height in the North Pacific Ocean (to the southeast of the Hawaiian Islands), mesoscale eddies move from east to west and are larger to the south. Two reports in this issue show that such eddies have very high biological activity. [Images from (*10*)]

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At the same time, some previously ignored modes of metabolism, such as nitrogen fixation were found to be more common than expected, and several groups made tantalizing observations of rare bursts of biogeochemical activity associated with eddies (*6*–*9*).

The introduction of new satellite sensors in the 1980s and 1990s exposed oceanography to synoptic views of the sea. It became clear that oceanographers were sampling a highly heterogeneous system, full of important structure that had previously been dismissed as random variability. Measurements of sea surface height (see the figure) clearly showed eddies. Model results suggested that these structures create local areas with increased nutrient supply into the lighted surface waters and patches of enhanced biological activity.

Could the biological activity in eddies be great enough to make up the rest of the difference between bottles and basins? The results reported by McGillicuddy *et al.* on page 1021 of this issue (*1*) suggest that they may. The authors show that eddies in the Atlantic can have enough biological activity in a few months to account for the productivity seen in the average patch of water of the same size over the course of a year or more.

However, not all eddies lead to the same biogeochemical outcomes. On page 1017, Benitez-Nelson *et al.* (*2*) study a persistent cold-core eddy off of Hawaii. It has a plankton bloom with high productivity. In both the Atlantic and Pacific Oceans, diatoms—unicellular plants with a silicious skeleton that are important in creating large sinking fluxes of organic matter—are key organisms. Yet, in the Hawaii eddy, most of the organic matter created by the bloom was still in the surface waters at the end of their period of observation rather than being transported into the deep sea.

The two reports demonstrate that ocean scientists can finally—with intensive observations, tracers, satellites, and models—find, track, and comprehensively sample mesoscale eddies. They also show that these important features of the ocean system are hotspots of rapid biological rates and geochemical transformations that begin to close the historical gap between measurements on local and basin scales.

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10.1126/science.1140059

PLANETARY SCIENCE

The Shifting Sands of Asteroids

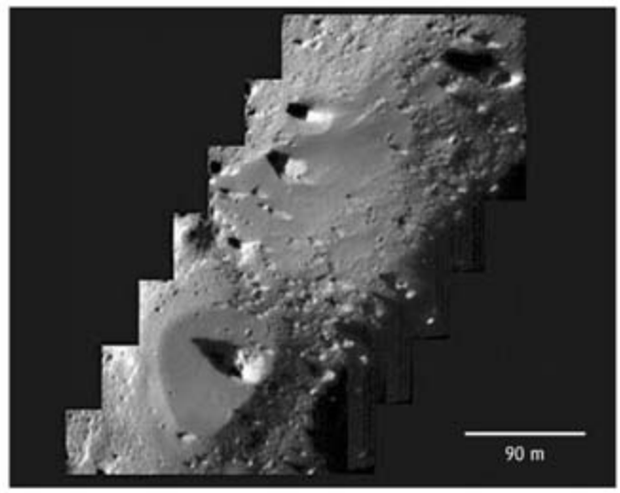
A tiny asteroid, expected to be solid, turns out to be an active pile of gravel.

Erik Asphaug

Although we are growing accustomed to asteroids defying our intuition, the report by Miyamoto *et al.* on page 1011 of this issue (*1*), that some small asteroids appear to be clumps of gravel, should come as no small surprise. 433 Eros, the ~33-km-long potato-shaped asteroid visited by NASA's Near Earth Asteroid Rendezvous (NEAR) mission 7 years ago (see the first figure), was originally thought to be a monolithic rock (*2*), but it turned out to be a shattered mass (*3*) with seas of mobile regolith (that is, surface dust, gravel, and blocks) (*4*). As the Japan Aerospace Exploration Agency's Hayabusa spacecraft approached the much smaller asteroid 25143 Itokawa (*5*) in 2005, the expectation was more guarded, but one could hardly help but think that with gravity only a few millionths that of Earth—1/100th that of Eros—we would discover an intact nugget. Au contraire. The Hayabusa mission has provided greater evidence than ever for pervasive, global-scale gravity control, leading us to wonder: Are any asteroids monolithic? And if not, what happens when we try to push on one in earnest, as may be required to divert a hazardous asteroid or to corral a resource-rich one into a beneficial orbit?

When NASA's Dawn mission (*6*, *7*) arrives at asteroid 4 Vesta in 2011, it will find a world with gigantic volcanic edifices and complex craters. Arriving at 1 Ceres in 2015, it might find relics of vast hydrological systems. Only a handful, at best, of the hundreds of thousands of objects that orbit the Sun inside Jupiter's path have undergone this kind of planetary processing; the rest have been cold, battered objects since the solar system's origin.

The first pictures of asteroids, obtained by spacecraft flybys in the 1990s (*8*, *9*), were of objects at the large end of the scale, tens of kilometers, because only these at the time had the accurately determined orbits required for a successful flyby. Smaller, much more common bodies occasionally come close enough to Earth to be imaged by ground-based radar telescopes (*10*); radar technology has revealed a representative menagerie (*11*) with sizes ranging down to tens of meters. With Hayabusa's arrival at Itokawa (dimensions ~0.5 by 0.2 by 0.3 km), we have visited the first small one, and perhaps the first typical one. It is a different kind of animal.



Abyssal asteroids. Seas and beaches on asteroid 433 Eros, from the NASA NEAR mission. Asteroid Itokawa, as imaged by Miyamoto *et al.*, appears to be an even more exotic gravel ball.

Most small asteroids have irregular shapes, and many rotate at the limit of flying apart (*12*, *13*). A fifth of known asteroids have flung off sizable moons during collisions or close tidal passages (*14*). They are geologically quite odd. Moreover, their geological

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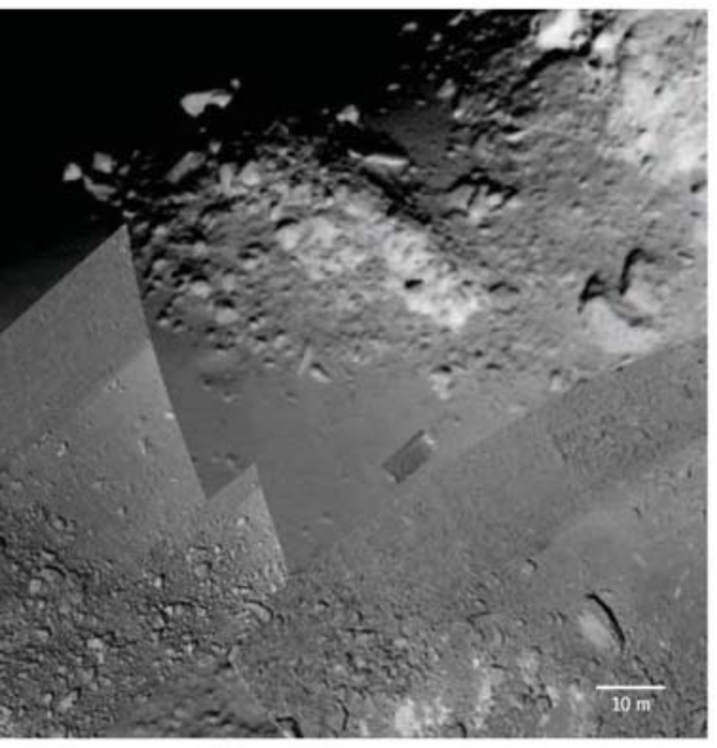
processes operate in an environment as weightless as that experienced by astronauts in low-Earth orbit, resulting in complex and mysterious landforms that beckon exploration. When Hayabusa touched down for sample return attempts (*15*) on 19 and 25 November 2005, it acquired close-up images with resolution of less than a centimeter, limited only by the focal length of the optics (see the second figure). Miyamoto *et al.* (*1*) now interpret these images of rocks and their emplacement, and the morphology of flat gravel expanses, as evidence for widespread granular sorting and convection—phenomena familiar on Earth and Mars but surprising to find on a celestial body the size of a few city blocks.

As is the case with most discovery reports, Miyamoto *et al.* include some thoughtful speculation along with their data. And as with any new science regarding asteroids, the reader should keep an open mind. But their interpretation, that Itokawa is a granular convective solid at global scales, is worthy of serious contemplation. If global-scale granular convective transport is a fundamental geophysical process on small asteroids, this represents a complete reversal of 30 years of thought. Small asteroids are not nuggets of rock. They have more in common with sedimentary basins, abyssal plains, and river channels.

The flat expanses on asteroids Itokawa and Eros (the only two asteroids orbited so far) are in fact called "seas." The seas on Eros even have margins called "beaches" (*4*). Miyamoto *et al.* propose that the seas on Itokawa form as the fabric of convective overturn, somewhat analogous to how ocean basins form on Earth. Stacks of boulders pile up at the accretionary margins of this convection, like miniature mountain belts. Itokawa has long lost any internal heat source capable of driving convection; the energy source would have to be a granular thermal input associated with impacting meteoroids.

Features observed on Itokawa are proposed by Miyamoto *et al.* to be the same patterns observed in laboratory granule beds or in landslide deposits: the clustering and alignment of boulders where convection meets a boundary layer (a stranding surface), the apparent loss of fine particles to space or to the subsurface (size segregation), and the upstream sloping of proposed convective surfaces (seas).

Because the surface blocks of Itokawa appear relatively fresh and angular, the hypothesis of Miyamoto *et al.* requires convection to happen faster than the pitting and disruption by micrometeorites, and therefore, perhaps, a high seismic efficiency (Q). But a gravity wave is unlikely to exist on a small asteroid, and seismic waves are likely to break upon a granular, ultra-low gravity free surface, so Q can only be high in the deep interior, if there is such a thing. All other considerations aside, granular convective processing is favored by microgravity (*16*). A required check on Miyamoto's hypothesis is an energy balance computation to see if the impact flux can really drive this kind of evolution. A well-observed cratering event involving a few kilograms of explosives might be justified.



Boulders all the way down? Asteroid Itokawa's surface shows patterns familiar in convective gravel beds and landslide deposits on Earth.

Granular materials behave both as solids and as liquids (*17*), and their study is at that stage where breakthroughs occur annually and where exotic behavior is the subject of much debate. Whenever young and active sciences meet—in this case, asteroid geophysics and granular mechanics—the result is often a whole new understanding of how things work. It is conceivable, for example, that the detailed study of granular flows at geologic scales, but in ~10^{-5} gravity, will unlock the secrets of landslides. As for the holy grail of granular physics, a thermodynamic formulation akin to the theory of gases, this might evolve through the study of microgravity flows and shaking/settling phenomena on bodies the size of Itokawa.

Earth and its rocky companions accreted in 10 to 30 million years following the Sun's formation. Impacts from gentle to gargantuan left behind billions of asteroids that were later swept up or scattered away. What survives is a winnowed population, like so many kernels of wheat in a sieve. Small asteroids are granules upon granules, themselves winnowed over time as their rocks overturn, bringing small particles to the surface that are swept away by solar radiation against minuscule self-gravity. The revelation that asteroids, the building blocks of planets, are continually evolving in this manner brings to mind the quote from Victor Hugo's *Les Miserables* that prefaced the classic review by Jaeger *et al.* (*17*) of granular mechanics, a discipline now perhaps wedded to asteroid mechanics: "How do we know that the creation of worlds is not determined by the fall of grains of sand?"

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RETROSPECTIVE

Francis Clark Howell (1925–2007)

Phillip V. Tobias

Clarity and careful synthesis enabled Francis Clark Howell to sort out anthropological puzzles, from Neandertals in Europe to hominids in Africa.

Francis Clark Howell was 81 years old when he succumbed to cancer on 10 March 2007. In an active career spanning more than 50 years, he had become a leading figure—arguably the leading figure—in the interlocking fields of paleoanthropology and paleontology. More than most of his contemporaries, he saw the study of human evolution as a multifaceted and multidisciplinary endeavor. As a result, he became steeped in the anatomy, geology, dating, archaeology, comparative paleontology, and ecology related to fossil hominids, and applied this versatility to enrich the interpretation of fossil hominid sites in Europe, Asia, and Africa.

Howell was born in Kansas City, Missouri, on 27 November 1925. After serving in the United States Navy in the Pacific Theater from 1944 to 1946, Howell began his higher education when he entered the University of Chicago in January 1947.

Save for a 2-year stint in the Anatomy Department of Washington University, St. Louis, Missouri (from 1953 to 1955), Howell was to spend 25 years in the Department of Anthropology at the University of Chicago. There, under Sherwood L. Washburn, he obtained his Ph.B., A.M., and Ph.D. degrees. He rose to become professor of anthropology in 1962 and chairman of the department in 1966. The second major phase of his career began in 1970 when he moved to the Department of Anthropology at the University of California, Berkeley, to which Washburn had earlier relocated. He spent the next 37 years at Berkeley, 21 years as professor of anthropology, and 16 years as professor emeritus, a position he held until his death.

In 1953 Howell began a series of work travels abroad. From then until 2005, scarcely a year elapsed without his traveling to often remote areas in Europe, Africa, and Asia. In the first cycle of travels, he devoted himself to the Neandertal fossils and their discovery sites in Europe. He claimed that the later (Classic) Neandertals developed their extreme features amid—

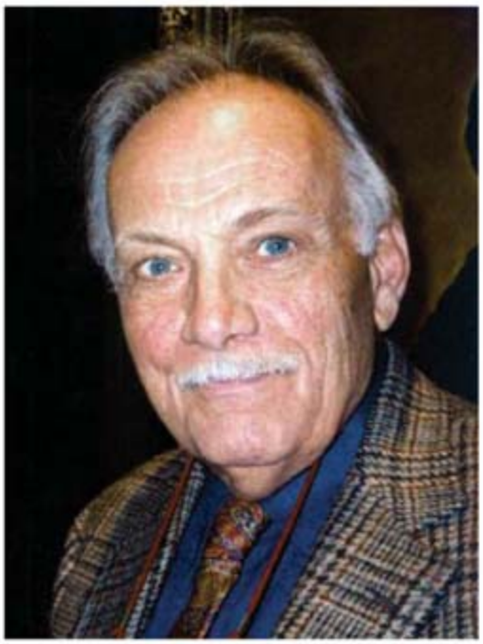

PHOTO CREDIT: TIM WHITE AND THE HOWELL FAMILY

and in response to—periglacial ecology. Howell's work on the Neandertals during this era might not pass muster in its pristine state today, having preceded the application of genetics and DNA to the study of human evolution. But the enduring lesson he taught was that the anatomy of fossil hominids was not to be considered in a vacuum but in an ecological, geological, and geographical setting.

In 1954 Howell extended his paleontological study tours to Africa—from Uganda, Kenya, and Tanzania to South Africa. He was always a cautious scientist, in a field in which many threw caution to the winds in favor of intemperate claims. We were examining the mandible of a hominid found at Swartkrans, South Africa, in 1949, and I was doubtful of the wisdom of the new generic status Broom and Robinson had assigned to the Swartkrans specimen. I asked Howell whether he agreed that a new genus was justified. He demurred, but it would have been wrong to interpret his reply as a sign of irresolution: He weighed his words carefully, and this was indeed part of his strength.

His wide-ranging travels enabled him to effect syntheses within many areas of anthropology. At Isimila, an Acheulean (260,000 years old) prehistoric occupation site in the Iringa highlands of central Tanzania, he recovered enormous hand-axes (1957 to 1958). Other examples were the Acheulean sites of Torralba and Ambrona (300,000 to 400,000 years old) in Spain (1961 to 1963). These meticulous excavations were marked by his customary many-sided approach. Sadly, at a time when scholars lacked human skeletal remains of the fabricators of the Acheulean, none of these excavations brought forth such remains, even though the cultural signs of hominid settlements were abundantly in evidence.

In this respect, Howell's fortunes changed when he turned his attention to Ethiopia. He made surveys of fossil-bearing lower Pleistocene (2.1 to 0.1 million years ago) beds in the Omo River region of southern Ethiopia in 1959 and again in 1966. The open-air deposits straddling the Omo River brought to light numbers of fossil vertebrates, including monkeys and hominids. The superb stratigraphy of the Omo basin, its fossiliferous strata interlarded with lava flows and volcanic ash layers or tuffs, provided a virtually ideal situation for the application of what were then fairly new dating methods, based on potassium-argon and other radio-isotopic techniques. It was perhaps the most productive and innovative phase of Howell's career.

Howell's consummate skill in tidying up messy areas of his fields was perhaps best revealed in his 95-page contribution to the compendious *Evolution of African Mammals*, edited by Vincent Maglio and Basil Cooke (1978). His chapter is entitled *Hominidae*. It is a model of elegance and simplicity and, although almost 30 years have elapsed since it was published, much of it is still valid. Of its kind, it provides a prototype for students and scholars of today.

It is a quaint custom in paleontology to name a new species after one who has attained distinction in the discipline—or was responsible for excavating or discovering the specimen(s) in question. No fewer than seven species, two of invertebrate gastropods and five of fossil mammals, received the species name (or in one instance the subspecies name) *howelli*. Even if this is not a record, it is surely a multiple tribute.

Clark Howell's departure from the scene has left the discipline the poorer and his colleagues and family grievously bereft.

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Childhood Origins of Adult Resistance to Science

Paul Bloom and Deena Skolnick Weisberg

Resistance to certain scientific ideas derives in large part from assumptions and biases that can be demonstrated experimentally in young children and that may persist into adulthood. In particular, both adults and children resist acquiring scientific information that clashes with common-sense intuitions about the physical and psychological domains. Additionally, when learning information from other people, both adults and children are sensitive to the trustworthiness of the source of that information. Resistance to science, then, is particularly exaggerated in societies where nonscientific ideologies have the advantages of being both grounded in common sense and transmitted by trustworthy sources.

Scientists, educators, and policy-makers have long been concerned about American adults' resistance to certain scientific ideas (*1*). In a 2005 Pew Trust poll, 42% of respondents said that they believed that humans and other animals have existed in their present form since the beginning of time, a view that denies the very existence of evolution (*2*). Even among the minority who claim to accept natural selection, most misunderstand it, seeing evolution as a mysterious process causing animals to have offspring that are better adapted to their environments (*3*). This is not the only domain where people reject science: Many believe in the efficacy of unproven medical interventions; the mystical nature of out-of-body experiences; the existence of supernatural entities such as ghosts and fairies; and the legitimacy of astrology, ESP, and divination (*4*). This resistance to science has important social implications, because a scientifically ignorant public is unprepared to evaluate policies about global warming, vaccination, genetically modified organisms, stem cell research, and cloning (*1*).

Here we review evidence from developmental psychology suggesting that some resistance to scientific ideas is a human universal. This resistance stems from two general facts about children, one having to do with what they know and the other having to do with how they learn.

The main source of resistance concerns what children know before their exposure to science. Recent psychological research makes it clear that babies are not "blank slates"; even 1-year-olds possess a rich understanding of both the physical world (a "naïve physics") and the social world (a "naïve psychology") (*5*). Babies know that objects are solid, persist over time (even when out of sight), fall to the ground if unsupported, and do not move unless acted upon (*6*). They also understand that people move autonomously in response to social and physical events, act and react in accord with their goals, and respond with appropriate emotions to different situations (*5*, *7*, *8*).

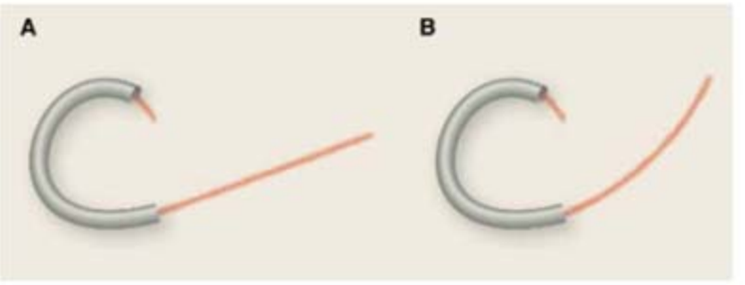

Fig. 1. (**A** and **B**) Alternative intuitions about the movement of a ball out of a curved tube [from (*13*)].

These intuitions give children a head start when it comes to understanding and learning about objects and people. However, they also sometimes clash with scientific discoveries about the nature of the world, making certain scientific facts difficult to learn. The problem with teaching science to children is thus "not what the student lacks, but what the student *has*, namely alternative conceptual frameworks for understanding the phenomena covered by the theories we are trying to teach" (*9*).

Children's belief that unsupported objects fall downward, for instance, makes it difficult for them to see the world as a sphere—if it were a sphere, the people and things on the other side should fall off. It is not until about 8 or 9 years of age that children demonstrate a coherent understanding of a spherical Earth (*10*), and younger children often distort the scientific understanding in systematic ways. Some deny that people can live all over Earth's surface (*10*), and when asked to draw Earth (*11*) or model it with clay (*12*), some children depict it as a sphere with a flattened top or as a hollow sphere that people live inside.

In some cases, there is such resistance to science education that it never entirely sticks, and foundational biases persist into adulthood. One study tested college undergraduates' intuitions about basic physical motions, such as the path that a ball will take when released from a curved tube (*13*). Many of the undergraduates retained a common-sense Aristotelian theory of object motion; they predicted that the ball would continue to move in a curved motion, choosing B over A in Fig. 1. An interesting addendum is that although education does not shake this bias, real-world experience can suffice. In another study, undergraduates were asked about the path that water would take out of a curved hose. This corresponded to an event that the participants had seen, and few believed that the water would take a curved path (*14*).

The examples so far concern people's common-sense understanding of the physical world, but their intuitive psychology also contributes to their resistance to science. One important bias is that children naturally see the world in terms of design and purpose. For instance, 4-year-olds insist that everything has a purpose, including lions ("to go in the zoo") and clouds ("for raining"), a propensity called "promiscuous teleology" (*15*). Additionally, when asked about the origin of animals and people, children spontaneously tend to provide and prefer creationist explanations (*16*). Just as children's intuitions about the physical world make it difficult for them to accept that Earth is a sphere, their psychological intuitions about agency and design make it difficult for them to accept the processes of evolution.

Another consequence of people's common-sense psychology is dualism, the belief that the mind is fundamentally different from the brain (*5*). This belief comes naturally to children. Preschool children will claim that the brain is responsible for some aspects of mental life, typically those involving deliberative mental work, such as solving math problems. But preschoolers will also claim that the brain is not involved in a host of other activities, such as pretending to be a kangaroo, loving one's brother, or brushing one's teeth (*5*, *17*). Similarly, when told about a brain transplant from a boy to a pig, they believed that you would get a very smart pig, but one with pig beliefs and pig desires (*18*). For young children, then, much of mental life is not linked to the brain.

The strong intuitive pull of dualism makes it difficult for people to accept what Francis Crick

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called "the astonishing hypothesis" (*19*): Dualism is mistaken—mental life emerges from physical processes. People resist the astonishing hypothesis in ways that can have considerable social implications. For one thing, debates about the moral status of embryos, fetuses, stem cells, and nonhuman animals are sometimes framed in terms of whether or not these entities possess immaterial souls (*20*, *21*). What's more, certain proposals about the role of evidence from functional magnetic resonance imaging in criminal trials assume a strong form of dualism (*22*). It has been argued, for instance, that if one could show that a person's brain is involved in an act, then the person himself or herself is not responsible, an excuse dubbed "my brain made me do it" (*23*). These assumptions about moral status and personal responsibility reflect a profound resistance to findings from psychology and neuroscience.

The main reason why people resist certain scientific findings, then, is that many of these findings are unnatural and unintuitive. But this does not explain cultural differences in resistance to science. There are substantial differences, for example, in how quickly children from different countries come to learn that Earth is a sphere (*10*). There is also variation across countries in the extent of adult resistance to science, including the finding that Americans are more resistant to evolutionary theory than are citizens of most other countries (*24*).

Part of the explanation for such cultural differences lies in how children and adults process different types of information. Some culture-specific information is not associated with any particular source; it is "common knowledge." As such, learning of this type of information generally bypasses critical analysis. A prototypical example is that of word meanings. Everyone uses the word "dog" to refer to dogs, so children easily learn that this is what they are called (*25*). Other examples include belief in germs and electricity. Their existence is generally assumed in day-to-day conversation and is not marked as uncertain; nobody says that they "believe in electricity." Hence, even children and adults with little scientific background believe that these invisible entities really exist (*26*).

Other information, however, is explicitly asserted, not tacitly assumed. Such asserted information is associated with certain sources. A child might note that science teachers make surprising claims about the origin of human beings, for instance, whereas their parents do not. Furthermore, the tentative status of this information is sometimes explicitly marked; people will assert that they "believe in evolution."

When faced with this kind of asserted information, one can occasionally evaluate its truth directly. But in some domains, including much of science, direct evaluation is difficult or impossible. Few of us are qualified to assess claims about the merits of string theory, the role of mercury in the etiology of autism, or the existence of repressed memories. So rather than evaluating the asserted claim itself, we instead evaluate the claim's source. If the source is deemed trustworthy, people will believe the claim, often without really understanding it. Consider, for example, that many Americans who claim to believe in natural selection are unable to accurately describe how natural selection works (*3*). This suggests that their belief is not necessarily rooted in an appreciation of the evidence and arguments. Rather, this scientifically credulous subpopulation accepts this information because they trust the people who say it is true.

Science is not special here; the same process of deference holds for certain religious, moral, and political beliefs as well. In an illustrative recent study, participants were asked their opinion about a social welfare policy that was described as being endorsed by either Democrats or Republicans. Although the participants sincerely believed that their responses were based on the objective merits of the policy, the major determinant of what they thought of the policy was, in fact, whether or not their favored political party was said to endorse it (*27*). Additionally, many of the specific moral intuitions held by members of a society appear to be the consequence, not of personal moral contemplation, but of deference to the views of the community (*28*).

Adults thus rely on the trustworthiness of the source when deciding which asserted claims to believe. Do children do the same? Recent studies suggest that they do; children, like adults, have at least some capacity to assess the trustworthiness of their information sources. Four- and five-year-olds, for instance, know that adults know things that other children do not (like the meaning of the word "hypochondriac") (*29*), and when given conflicting information from a child and from an adult, they prefer to learn from the adult (*30*). They know that adults have different areas of expertise: Doctors know how to fix broken arms, and mechanics know how to fix flat tires (*31*, *32*). They prefer to learn from a knowledgeable speaker than from an ignorant one (*29*, *33*), and they prefer a confident source to a tentative one (*34*). Finally, when 5-year-olds hear about a competition whose outcome was unclear, they are more likely to believe a person who claimed that he had lost the race (a statement that goes against his self-interest) than a person who claimed that he had won the race (a statement that goes with his self-interest). In a limited sense, then, they are capable of cynicism (*35*).

These developmental data suggest that resistance to science will arise in children when scientific claims clash with early emerging, intuitive expectations. This resistance will persist through adulthood if the scientific claims are contested within a society, and it will be especially strong if there is a nonscientific alternative that is rooted in common sense and championed by people who are thought of as reliable and trustworthy. This is the current situation in the United States, with regard to the central tenets of neuroscience and evolutionary biology. These concepts clash with intuitive beliefs about the immaterial nature of the soul and the purposeful design of humans and other animals, and (in the United States) these beliefs are particularly likely to be endorsed and transmitted by trusted religious and political authorities (*24*). Hence, these fields are among the domains where Americans' resistance to science is the strongest.

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The New Synthesis in Moral Psychology

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People are selfish, yet morally motivated. Morality is universal, yet culturally variable. Such apparent contradictions are dissolving as research from many disciplines converges on a few shared principles, including the importance of moral intuitions, the socially functional (rather than truth-seeking) nature of moral thinking, and the coevolution of moral minds with cultural practices and institutions that create diverse moral communities. I propose a fourth principle to guide future research: Morality is about more than harm and fairness. More research is needed on the collective and religious parts of the moral domain, such as loyalty, authority, and spiritual purity.

If you ever become a contestant on an unusually erudite quiz show, and you are asked to explain human behavior in two seconds or less, you might want to say "self-interest." After all, economic models that assume only a motive for self-interest perform reasonably well. However, if you have time to give a more nuanced answer, you should also discuss the moral motives addressed in Table 1. Try answering those questions now. If your total for column B is higher than your total for column A, then congratulations, you are *Homo moralis*, not *Homo economicus*. You have social motivations beyond direct self-interest, and the latest research in moral psychology can help explain why.

In 1975, E. O. Wilson (*1*) predicted that ethics would soon be incorporated into the "new synthesis" of sociobiology. Two psychological theories of his day were ethical behaviorism (values are learned by reinforcement) and the cognitive-developmental theory of Lawrence Kohlberg (social experiences help children construct an increasingly adequate understanding of justice). Wilson believed that these two theories would soon merge with research on the hypothalamic-limbic system, which he thought supported the moral emotions, to provide a comprehensive account of the origins and mechanisms of morality.

As it turned out, Wilson got the ingredients wrong. Ethical behaviorism faded with behaviorism. Kohlberg's approach did grow to dominate moral psychology for the next 15 years, but because Kohlberg focused on conscious verbal reasoning, Kohlbergian psychology forged its interdisciplinary links with philosophy and education, rather than with biology as Wilson had hoped. And finally, the hypothalamus was found to play little role in moral judgment.

Despite these errors in detail, Wilson got the big picture right. The synthesis began in the 1990s with a new set of ingredients, and it has transformed the study of morality today. Wilson was also right that the key link between the social and natural sciences was the study of emotion and the "emotive centers" of the brain. A quantitative analysis of the publication database in psychology shows that research on morality and emotion grew steadily in the 1980s and 1990s (relative to other topics), and then grew very rapidly in the past 5 years (fig. S1).

In this Review, I suggest that the key factor that catalyzed the new synthesis was the "affective revolution" of the 1980s—the increase in research on emotion that followed the "cognitive revolution" of the 1960s and 1970s. I describe three principles, each more than 100 years old, that were revived during the affective revolution. Each principle links together insights from several fields, particularly social psychology, neuroscience, and evolutionary theory. I conclude with a fourth principle that I believe will be the next step in the synthesis.

Principle 1: Intuitive Primacy (but Not Dictatorship)

Kohlberg thought of children as budding moral philosophers, and he studied their reasoning as they struggled with moral dilemmas (e.g., Should a man steal a drug to save his wife's life?). But in recent years, the importance of moral reasoning has been questioned as social psychologists have increasingly embraced a version of the "affective primacy" principle, articulated in the 1890s by Wilhelm Wundt and greatly expanded in 1980 by Robert Zajonc (*2*). Zajonc reviewed evidence that the human mind is composed of an ancient, automatic, and very fast affective system and a phylogenetically newer, slower, and motivationally weaker cognitive system. Zajonc's basic point was that brains are always and automatically evaluating everything they perceive, and that higher-level human thinking is preceded, permeated, and influenced by affective reactions (simple feelings of like and dislike) which push us gently (or not so gently) toward approach or avoidance.

Evolutionary approaches to morality generally suggest affective primacy. Most propose that the building blocks of human morality are emotional (*3*, *4*) (e.g., sympathy in response to suffering, anger at nonreciprocators, affection for kin and allies) and that some early forms of these building blocks were already in place before the hominid line split off from that of *Pan* 5 to 7 million years ago (*5*). Language and the ability to engage in conscious moral reasoning came much later, perhaps only in the past 100 thousand years, so it is implausible that the neural mechanisms that control human judgment and behavior were suddenly rewired to hand control of the organism over to this new deliberative faculty.

Social-psychological research strongly supports Zajonc's claims about the speed and ubiquity of affective reactions (*6*). However, many have objected to the contrast of "affect" and "cognition," which seems to imply that affective reactions don't involve information processing or computation of any kind. Zajonc did not say that, but to avoid ambiguity I have drawn on the work of Bargh (*7*) to argue that the most useful contrast for moral psychology is between two kinds of cognition: moral intuition and moral reasoning (*8*). Moral intuition refers to fast, automatic, and (usually) affect-laden processes in which an evaluative feeling of good-bad or like-dislike (about the actions or character of a person) appears in consciousness without any awareness of having gone through steps of search, weighing evidence, or inferring a conclusion. Moral reasoning, in contrast, is a controlled and "cooler" (less affective) process; it is conscious mental activity that consists of transforming information about people and their actions in order to reach a moral judgment or decision.

My attempt to illustrate the new synthesis in moral psychology is the Social Intuitionist Model (*8*), which begins with the intuitive primacy principle. When we think about sticking a pin into a child's hand, or we hear a story about a person slapping her father, most of us have an automatic intuitive reaction that includes a flash of negative affect. We often engage in conscious verbal reasoning too, but this controlled process can occur only after the first automatic process has run, and it is often influenced by the initial moral intuition. Moral reasoning, when it occurs, is usually a post-hoc process in which we search for evidence to support our initial intuitive reaction.

Evidence that this sequence of events is the standard or default sequence comes from studies indicating that (i) people have nearly instant implicit reactions to scenes or stories of moral violations (*9*); (ii) affective reactions are usually good predictors of moral judgments and behaviors (*10*, *11*); (iii) manipulating emotional reactions, such as through hypnosis, can alter moral judgments (*12*); and (iv) people can sometimes be "morally dumbfounded"—they can know intuitively that something is wrong, even when they cannot explain why (*8*, *13*). Furthermore, studies of everyday reasoning (*14*) demonstrate that people generally begin reasoning by setting out to confirm their initial hypothesis. They rarely seek disconfirming evidence, and are quite good at finding support for whatever they want to believe (*15*).

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The importance of affect-laden intuitions is a central theme of neuroscientific work on morality. Damasio (*16*) found that patients who had sustained damage to certain areas of the prefrontal cortex retained their "cognitive" abilities by most measures, including IQ and explicit knowledge of right and wrong, but they showed massive emotional deficits, and these deficits crippled their judgment and decision-making. They lost the ability to feel the normal flashes of affect that the rest of us feel when we simply hear the words "slap your father." They lost the ability to use their bodies—or, at least, to integrate input from brain areas that map bodily reactions—to feel what they would actually feel if they were in a given situation. Later studies of moral judgment have confirmed the importance of areas of the medial prefrontal cortex, including ventromedial prefrontal cortex and the medial frontal gyrus (*17*, *18*). These areas appear to be crucial for integrating affect (including expectations of reward and punishment) into decisions and plans. Other areas that show up frequently in functional magnetic resonance imaging studies include the amygdala and the frontal insula (*9*, *11*, *16*). These areas seem to be involved in sounding a kind of alarm, and for then "tilting the pinball machine," as it were, to push subsequent processing in a particular direction.

Table 1. What's your price? Write in the minimum amount that someone would have to pay you (anonymously and secretly) to convince you to do these 10 actions. For each one, assume there will be no social, legal, or material consequences to you afterward. *Homo economicus* would prefer the option in column B to the option in column A for action 1 and would be more or less indifferent to the other four pairs. In contrast, a person with moral motives would (on average) require a larger payment to engage in the actions in column B and would feel dirty or degraded for engaging in some of these actions for personal enrichment. These particular actions were generated to dramatize moral motives, but they also illustrate the five-foundations theory of intuitive ethics (*41*, *42*).

	How much money would it take to get you to...		
	Column A	Column B	Moral category
1)	Stick a pin into your palm. $___	Stick a pin into the palm of a child you don't know. $___	Harm/ care
2)	Accept a plasma screen television that a friend of yours wants to give you. You know that your friend got the television a year ago when the company that made it sent it, by mistake and at no charge, to your friend. $___	Accept a plasma screen television that a friend of yours wants to give you. You know that your friend bought the TV a year ago from a thief who had stolen it from a wealthy family. $___	Fairness/ reciprocity
3)	Say something slightly bad about your nation (which you don't believe to be true) while calling in, anonymously, to a talk-radio show in your nation. $___	Say something slightly bad about your nation (which you don't believe to be true) while calling in, anonymously, to a talk-radio show in a foreign nation. $___	Ingroup/ loyalty
4)	Slap a friend in the face (with his/her permission) as part of a comedy skit. $___	Slap your father in the face (with his permission) as part of a comedy skit. $___	Authority/ respect
5)	Attend a performance art piece in which the actors act like idiots for 30 min, including failing to solve simple problems and falling down repeatedly on stage. $___	Attend a performance art piece in which the actors act like animals for 30 min, including crawling around naked and urinating on stage. $___	Purity/ sanctity
	Total for column A: $___	Total for column B: $___	

Affective reactions push, but they do not absolutely force. We can all think of times when we deliberated about a decision and went against our first (often selfish) impulse, or when we changed our minds about a person. Greene *et al.* (*19*) caught the brain in action overriding its initial intuitive response. They created a class of difficult dilemmas, for example: Would you smother your own baby if it was the only way to keep her from crying and giving away your hiding place to the enemy soldiers looking for you, who would then kill the whole group of you hiding in the basement? Subjects were slow to respond to cases like these and, along the way, exhibited increased activity in the anterior cingulate cortex, a brain region that responds to internal conflict. Some subjects said "yes" to cases like these, and they exhibited increased activity in the dorsolateral prefrontal cortex, suggesting that they were doing additional processing and overriding their initial flash of horror.

There are at least three ways we can override our immediate intuitive responses. We can use conscious verbal reasoning, such as considering the costs and benefits of each course of action. We can reframe a situation and see a new angle or consequence, thereby triggering a second flash of intuition that may compete with the first. And we can talk with people who raise new arguments, which then trigger in us new flashes of intuition followed by various kinds of reasoning. The social intuitionist model includes separate paths for each of these three ways of changing one's mind, but it says that the first two paths are rarely used, and that most moral change happens as a result of social interaction. Other people often influence us, in part by presenting the counterevidence we rarely seek out ourselves. Some researchers believe, however, that private, conscious verbal reasoning is either the ultimate authority or at least a frequent contributor to our moral judgments and decisions (*19*–*21*). There are at present no data on how people revise their initial judgments in everyday life (outside the lab), but we can look more closely at research on reasoning in general. What role is reasoning fit to play?

Principle 2: (Moral) Thinking Is for (Social) Doing

During the cognitive revolution, many psychologists adopted the metaphor that people are "intuitive scientists" who analyze the evidence of everyday experience to construct internal representations of reality. In the past 15 years, however, many researchers have rediscovered William James' pragmatist dictum that "thinking is for doing." According to this view, moral reasoning is not like that of an idealized scientist or judge seeking the truth, which is often useful; rather, moral reasoning is like that of a lawyer or politician seeking whatever is useful, whether or not it is true.

One thing that is always useful is an explanation of what you just did. People in all societies gossip, and the ability to track reputations and burnish one's own is crucial in most recent accounts of the evolution of human morality (*22*, *23*). The first rule of life in a dense web of gossip is: Be careful what you do. The second rule is: What you do matters less than what people think you did, so you'd better be able to frame your actions in a positive light. You'd better be a good "intuitive politician" (*24*). From this social-functionalist perspective, it is not surprising that people are generally more accurate in their predictions of what others will do than in their (morally rosier) predictions about what they themselves will do (*25*), and it is not

surprising that people so readily invent and confidently tell stories to explain their own behaviors (*26*). Such "confabulations" are often reported in neuroscientific work; when brain damage or surgery creates bizarre behaviors or beliefs, the patient rarely says "Gosh, why did I do that?" Rather, the patient's "interpreter module" (*27*) struggles heroically to weave a story that is then offered confidently to others. Moral reasoning is often like the press secretary for a secretive administration—constantly generating the most persuasive arguments it can muster for policies whose true origins and goals are unknown (*8*, *28*).

The third rule of life in a web of gossip is: Be prepared for other people's attempts to deceive and manipulate you. The press secretary's pronouncements usually contain some useful information, so we attend to them, but we don't take them at face value. We easily switch into "intuitive prosecutor" mode (*24*), using our reasoning capacities to challenge people's excuses and to seek out—or fabricate—evidence against people we don't like. Thalia Wheatley and I (*12*) recently created prosecutorial moral confabulations by giving hypnotizable subjects a post-hypnotic suggestion that they would feel a flash of disgust whenever they read a previously neutral word ("take" for half the subjects; "often" for the others). We then embedded one of those two words in six short stories about moral violations (e.g., accepting bribes or eating one's dead pet dog) and found that stories that included the disgust-enhanced word were condemned more harshly than those that had no such flash.

To test the limiting condition of this effect, we included one story with no wrongdoing, about Dan, a student council president, who organizes faculty-student discussions. The story included one of two versions of this sentence: "He [tries to take]/[often picks] topics that appeal to both professors and students in order to stimulate discussion." We expected that subjects who felt a flash of disgust while reading this sentence would condemn Dan (intuitive primacy), search for a justification (post-hoc reasoning), fail to find one, and then be forced to override their hypnotically induced gut feeling using controlled processes. Most did. But to our surprise, one third of the subjects in the hypnotic disgust condition (and none in the other) said that Dan's action was wrong to some degree, and a few came up with the sort of post-hoc confabulations that Gazzaniga reported in some split-brain patients, such as "Dan is a popularity-seeking snob" or "It just seems like he's up to something." They invented reasons to make sense of their otherwise inexplicable feeling of disgust.

When we engage in moral reasoning, we are using relatively new cognitive machinery that was shaped by the adaptive pressures of life in a reputation-obsessed community. We are capable of using this machinery dispassionately, such as when we consider abstract problems with no personal ramifications. But the machinery itself was "designed" to work with affect, not free of it, and in daily life the environment usually obliges by triggering some affective response. But how did humans, and only humans, develop these gossipy communities in the first place?

Principle 3: Morality Binds and Builds

Nearly every treatise on the evolution of morality covers two processes: kin selection (genes for altruism can evolve if altruism is targeted at kin) and reciprocal altruism (genes for altruism can evolve if altruism and vengeance are targeted at those who do and don't return favors, respectively). But several researchers have noted that these two processes cannot explain the extraordinary degree to which people cooperate with strangers they'll never meet again and sacrifice for large groups composed of nonkin (*23*, *29*). There must have been additional processes at work, and the study of these processes—especially those that unite cultural and evolutionary thinking —is an exciting part of the new synthesis. The unifying principle, I suggest, is the insight of the sociologist Emile Durkheim (*30*) that morality binds and builds; it constrains individuals and ties them to each other to create groups that are emergent entities with new properties.

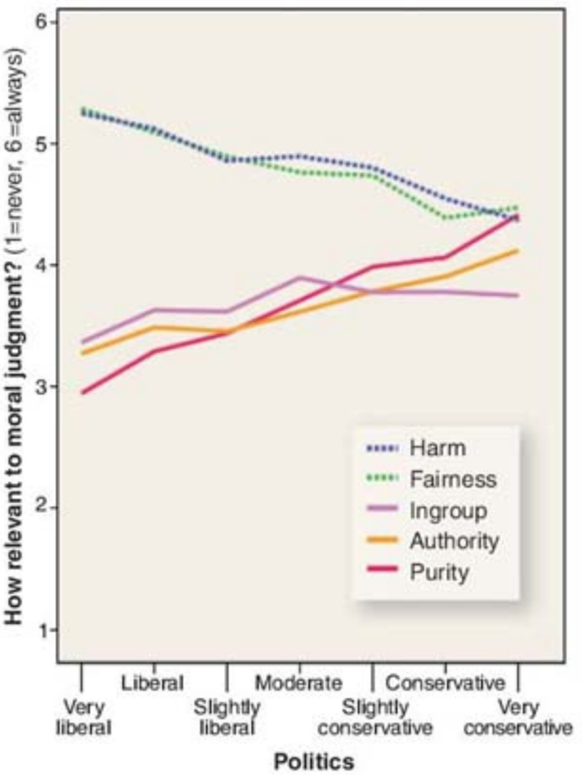

Fig. 1. Liberal versus conservative moral foundations. Responses to 15 questions about which considerations are relevant to deciding "whether something is right or wrong." Those who described themselves as "very liberal" gave the highest relevance ratings to questions related to the Harm/Care and Fairness/Reciprocity foundations and gave the lowest ratings to questions about the Ingroup/Loyalty, Authority/Respect, and Purity/Sanctity foundations. The more conservative the participant, the more the first two foundations decrease in relevance and the last three increase [n = 2811; data aggregated from two web surveys, partially reported in (*41*)]. All respondents were citizens of the United States. Data for 476 citizens of the United Kingdom show a similar pattern. The survey can be taken at www.yourmorals.org.

A moral community has a set of shared norms about how members ought to behave, combined with means for imposing costs on violators and/or channeling benefits to cooperators. A big step in modeling the evolution of such communities is the extension of reciprocal altruism by "indirect reciprocity" (*31*) in which virtue pays by improving one's reputation, which elicits later cooperation from others. Reputation is a powerful force for strengthening and enlarging moral communities (as users of ebay.com know). When repeated-play behavioral economics games allow players to know each others' reputations, cooperation rates skyrocket (*29*). Evolutionary models show that indirect reciprocity can solve the problem of free-riders (which doomed simpler models of altruism) in moderately large groups (*32*), as long as people have access to information about reputations (e.g., gossip) and can then engage in low-cost punishment such as shunning.

However the process began, early humans sometimes found ways to solve the free-rider problem and to live in larger cooperative groups. In so doing, they may have stepped through a major transition in evolutionary history (*33*). From prokaryotes to eukaryotes, from single-celled organisms to plants and animals, and from individual animals to hives, colonies, and cooperative groups, the simple rules of Darwinian evolution never change, but the complex game of life changes when radically new kinds of players take the field. Ant colonies are a kind of super-organism whose proliferation has altered the ecology of our planet. Ant colonies compete with each other, and group selection therefore shaped ant behavior and made ants extraordinarily cooperative within their colonies. However, biologists have long resisted the idea that group selection contributed to human altruism because human groups do not restrict breeding to a single queen or breeding pair. Genes related to altruism for the good of the group are therefore vulnerable to replacement by genes related to more selfish free-riding strategies. Human group selection was essentially declared off-limits in 1966 (*34*).

In the following decades, however, several theorists realized that human groups engage in cultural practices that modify the circumstances under which genes are selected. Just as a modified gene for adult lactose tolerance evolved

in tandem with cultural practices of raising dairy cows, so modified genes for moral motives may have evolved in tandem with cultural practices and institutions that rewarded group-beneficial behaviors and punished selfishness. Psychological mechanisms that promote uniformity within groups and maintain differences across groups create conditions in which group selection can occur, both for cultural traits and for genes (*23*, *35*). Even if groups vary little or not at all genetically, groups that develop norms, practices, and institutions that elicit more group-beneficial behavior can grow, attract new members, and replace less cooperative groups. Furthermore, preagricultural human groups may have engaged in warfare often enough that group selection altered gene frequencies as well as cultural practices (*36*). Modified genes for extreme group solidarity during times of conflict may have evolved in tandem with cultural practices that led to greater success in war.

Humans attain their extreme group solidarity by forming moral communities within which selfishness is punished and virtue rewarded. Durkheim believed that gods played a crucial role in the formation of such communities. He saw religion as "a unified system of beliefs and practices relative to sacred things, that is to say, things set apart and forbidden—beliefs and practices which unite into one single moral community called a church, all those who adhere to them" (*30*). D. S. Wilson (*35*) has argued that the coevolution of religions and religious minds created conditions in which multilevel group selection operated, transforming the older morality of small groups into a more tribal form that could unite larger populations. As with ants, group selection greatly increased cooperation within the group, but in part for the adaptive purpose of success in conflict between groups.

Whatever the origins of religiosity, nearly all religions have culturally evolved complexes of practices, stories, and norms that work together to suppress the self and connect people to something beyond the self. Newberg (*37*) found that religious experiences often involve decreased activity in brain areas that maintain maps of the self's boundaries and position, consistent with widespread reports that mystical experiences involve feelings of merging with God or the universe. Studies of ritual, particularly those involving the sort of synchronized motor movements common in religious rites, indicate that such rituals serve to bind participants together in what is often reported to be an ecstatic state of union (*38*). Recent work on mirror neurons indicates that, whereas such neurons exist in other primates, they are much more numerous in human beings, and they serve to synchronize our feelings and movements with those of others around us (*39*). Whether people use their mirror neurons to feel another's pain, enjoy a synchronized dance, or bow in unison toward Mecca, it is clear that we are prepared, neurologically, psychologically, and culturally, to link our consciousness, our emotions, and our motor movements with those of other people.

Principle 4: Morality Is About More Than Harm and Fairness

If I asked you to define morality, you'd probably say it has something to do with how people ought to treat each other. Nearly every research program in moral psychology has focused on one of two aspects of interpersonal treatment: (i) harm, care, and altruism (people are vulnerable and often need protection) or (ii) fairness, reciprocity, and justice (people have rights to certain resources or kinds of treatment). These two topics bear a striking match to the two evolutionary mechanisms of kin selection (which presumably made us sensitive to the suffering and needs of close kin) and reciprocal altruism (which presumably made us exquisitely sensitive to who deserves what). However, if group selection did reshape human morality, then there might be a kind of tribal overlay (*23*)—a coevolved set of cultural practices and moral intuitions—that are not about how to treat other individuals but about how to be a part of a group, especially a group that is competing with other groups.

In my cross-cultural research, I have found that the moral domain of educated Westerners is narrower—more focused on harm and fairness—than it is elsewhere. Extending a theory from cultural psychologist Richard Shweder (*40*), Jesse Graham, Craig Joseph, and I have suggested that there are five psychological foundations, each with a separate evolutionary origin, upon which human cultures construct their moral communities (*41*, *42*). In addition to the harm and fairness foundations, there are also widespread intuitions about ingroup-outgroup dynamics and the importance of loyalty; there are intuitions about authority and the importance of respect and obedience; and there are intuitions about bodily and spiritual purity and the importance of living in a sanctified rather than a carnal way. And it's not just members of traditional societies who draw on all five foundations; even within Western societies, we consistently find an ideological effect in which religious and cultural conservatives value and rely upon all five foundations, whereas liberals value and rely upon the harm and fairness foundations primarily (Fig. 1 and Table 1).

Research on morality beyond harm and fairness is in its infancy; there is much to be learned. We know what parts of the brain are active when people judge stories about runaway trolleys and unfair divisions of money. But what happens when people judge stories about treason, disrespect, or gluttony? We know how children develop an ethos of caring and of justice. But what about the development of patriotism, respect for tradition, and a sense of sacredness? There is some research on these questions, but it is not yet part of the new synthesis, which has focused on issues related to harm and fairness.

In conclusion, if the host of that erudite quiz show were to allow you 60 seconds to explain human behavior, you might consider saying the following: People are self-interested, but they also care about how they (and others) treat people, and how they (and others) participate in groups. These moral motives are implemented in large part by a variety of affect-laden intuitions that arise quickly and automatically and then influence controlled processes such as moral reasoning. Moral reasoning can correct and override moral intuition, though it is more commonly performed in the service of social goals as people navigate their gossipy worlds. Yet even though morality is partly a game of self-promotion, people do sincerely want peace, decency, and cooperation to prevail within their groups. And because morality may be as much a product of cultural evolution as genetic evolution, it can change substantially in a generation or two. For example, as technological advances make us more aware of the fate of people in faraway lands, our concerns expand and we increasingly want peace, decency, and cooperation to prevail in other groups, and in the human group as well.

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Supporting Online Material

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Figs. S1 and S2
References
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Embodying Emotion

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Recent theories of embodied cognition suggest new ways to look at how we process emotional information. The theories suggest that perceiving and thinking about emotion involve perceptual, somatovisceral, and motoric reexperiencing (collectively referred to as "embodiment") of the relevant emotion in one's self. The embodiment of emotion, when induced in human participants by manipulations of facial expression and posture in the laboratory, causally affects how emotional information is processed. Congruence between the recipient's bodily expression of emotion and the sender's emotional tone of language, for instance, facilitates comprehension of the communication, whereas incongruence can impair comprehension. Taken all together, recent findings provide a scientific account of the familiar contention that "when you're smiling, the whole world smiles with you."

Here is a thought experiment: A man goes into a bar to tell a new joke. Two people are already in the bar. One is smiling and one is frowning. Who is more likely to "get" the punch line and appreciate his joke? Here is another: Two women are walking over a bridge. One is afraid of heights, so her heart pounds and her hands tremble. The other is not afraid at all. On the other side of the bridge, they encounter a man. Which of the two women is more likely to believe that she has just met the man of her dreams?

You probably guessed that the first person of the pair described in each problem was the right answer. Now consider the following experimental findings:

1) While adopting either a conventional working posture or one of two so-called ergonomic postures, in which the back was straight and the shoulders were held high and back or in which the shoulders and head were slumped, experimental participants learned that they had succeeded on an achievement test completed earlier. Those who received the good news in the slumped posture felt less proud and reported being in a worse mood than participants in the upright or working posture (*1*).

2) Images that typically evoke emotionally "positive" and "negative" responses were presented on a computer screen. Experimental participants were asked to indicate when a picture appeared by quickly moving a lever. Some participants were instructed to push a lever away from their body, whereas others were told to pull a lever toward their body. Participants who pushed the lever away responded to negative images faster than to positive images, whereas participants who pulled the lever toward themselves responded faster to positive images (*2*).

3) Under the guise of studying the quality of different headphones, participants were induced either to nod in agreement or to shake their heads in disagreement. While they were "testing" their headphones with one of these two movements, the experimenter placed a pen on the table in front of them. Later, a different experimenter offered the participants the pen that had been placed on the table earlier or a novel pen. Individuals who were nodding their heads preferred the old pen, whereas participants who had been shaking their heads preferred the new one (*3*).

All of these studies show that there is a reciprocal relationship between the bodily expression of emotion and the way in which emotional information is attended to and interpreted (Fig. 1). Charles Darwin himself defined attitude as a collection of motor behaviors (especially posture) that conveys an organism's emotional response toward an object (*4*). Thus, it would not have come as any surprise to him that the human body is involved in the acquisition and use of attitudes and preferences. Indeed, one speculates that Darwin would be satisfied to learn that research reveals that (i) when individuals adopt emotion-specific postures, they report experiencing the associated emotions; (ii) when individuals adopt facial expressions or make emotional gestures, their preferences and attitudes are influenced; and (iii) when individuals' motor movements are inhibited, interference in the experience of emotion and processing of emotional information is observed (*5*). The causal relationship between embodying emotions, feeling emotional states,

Fig. 1. Two ways in which facial expression has been manipulated in behavioral experiments. (**Top**) In order to manipulate contraction of the brow muscle in a simulation of negative affect, researchers have affixed golf tees to the inside of participants' eyebrows (*42*). Participants in whom negative emotion was induced were instructed to bring the ends of the golf tees together, as in the right panel. [Photo credit: Psychology Press]. (**Bottom**) In other research, participants either held a pen between the lips to inhibit smiling, as in the left panel, or else held the pen between the teeth to facilitate smiling (*39*).

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and acquiring and using information about emotion is currently the subject of a substantial amount of research in psychology and neuroscience. The way to understand this relationship between bodily states of emotion and the manner in which humans encode, represent, and use emotional information is the topic of this article. In particular, I discuss insights that have been stimulated by theories of embodied cognition and show how such theories account for the embodiment effects that you and Darwin might have been able to intuit.

Emotions and Theories of Embodied Cognition

Until recently, psychologists and cognitive scientists have spent little effort on the development of complete models of the mental processing of emotional information. This is true in spite of the fact that such information prioritizes attention (*6*), access to word meaning (*7*), and the organization of material in memory (*8*). For many scientists, emotion has simply seemed fraught with too many difficulties to be considered as a tractable topic of study.

One way to avoid the problems in studying emotions is to make them go away. Classic models of information processing in the cognitive sciences allow sensory, motor, and emotional experience to be represented as stripped of their perceptual and experiential basis. In such models, largely inspired by the metaphor of "mind as computer," information taken in by the different sense modalities is preserved in memory in the form of abstract symbols. These are stored in a manner that is functionally separated from the original neural systems (those involved in vision, olfaction, and audition, for example) that encoded them in the first place [(*9*, *10*); see (*11*) and (*12*) for discussion]. Such information-processing models render what individuals know about emotion equivalent to what they know about most other things. Conveniently, the models also do away with the priority of emotion in information processing. And the sensory, motor, and affective systems are not required for thinking or language use.

There are other ways to think about information processing, and these ways are clustered under the label "theories of embodied cognition." Although this approach provides an original perspective and is based on methodological and technological innovation, the basic idea is actually very old (*13*). The assertion common to recent instantiations of such theories is that high-level cognitive processes (such as thought and language) use partial reactivations of states in sensory, motor, and affective systems to do their jobs (*14*). Put another way, the grounding for knowledge—what it refers to—is the original neural state that occurred when the information was initially acquired. If this is true, then using knowledge is a lot like reliving past experience in at least some (and sometimes all) of its sensory, motor, and affective modalities: The brain captures modality-specific states during perception, action, and interoception and then reinstantiates parts of the same states to represent knowledge when needed.

Theories of embodied cognition have now been applied to provide rigorous accounts of emotion and the processing of information about emotion (*5*, *15*). In this regard, experiencing an emotion, perceiving an emotional stimulus, and retrieving an emotional memory all involve highly overlapping mental processes. One schematic way that this might work is illustrated in Fig. 2. As depicted, the perception of an emotional stimulus, such as a snarling bear, involves, among other responses, seeing, hearing, and feeling consciously afraid of the bear. Altogether, the neural, bodily, and subjective feeling state might be called "fear" for the perceiver (although the same patterns might be called "exhilaration" for another perceiver or for the same perceiver in a different context). Populations of neurons in the modality-specific sensory, motor, and affective systems are highly interconnected, and their activation supports the integrated, multimodal experience of the bear.

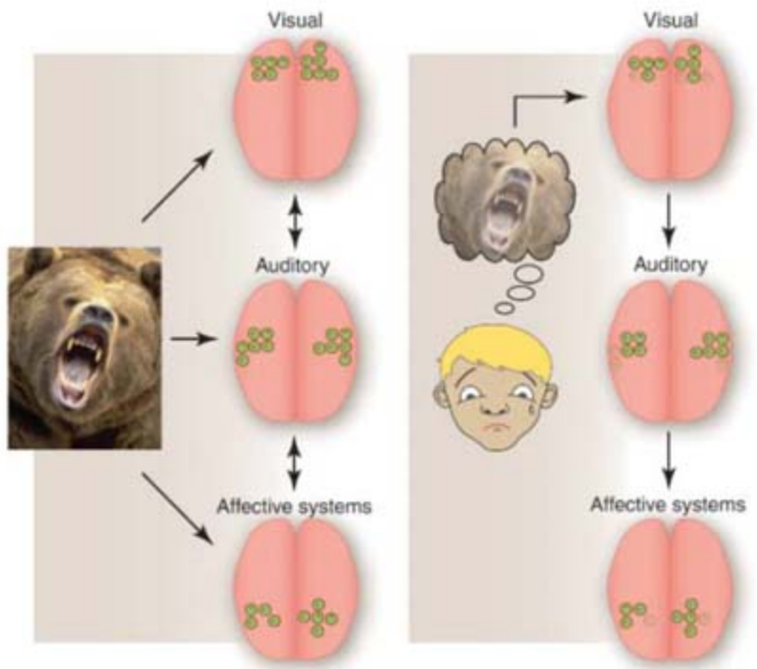

Fig. 2. (**Left**) Activation of populations of neurons on visual, auditory, and affective systems upon perception of the snarling bear is illustrated schematically. (**Right**) Later, when remembering the appearance of the bear, parts of the original states of the visual system are reinstated. These then can act to reactivate the parts of the states that were originally active in the other systems (*5*). [Photo credit: Jim Zuckerman/CORBIS]

Later, in just thinking about stumbling on the bear, the neural states that represent (for example) the visual impression of the bear can be reactivated. The reinstantiation of a pattern of neurons in one system can then cascade to complete the full pattern in the others. Through the interconnections of the populations of neurons that were active during the original experience, a partial multimodal reenactment of the experience is produced (*16*, *17*). Critically for such an account, one reason that only parts of the original neural states are reactivated is that attention is selectively focused on the aspects of the experience that are most salient and important for the individual. These then are the aspects that are most likely to be stored for later reactivation (*12*). Because emotions are salient and functional, this aspect of experience will certainly be preserved (*8*).

In theories of embodied cognition, using knowledge—as in recalling memories, drawing inferences, and making plans—is thus called "embodied" because an admittedly incomplete but cognitively useful reexperience is produced in the originally implicated sensory-motor systems, as if the individual were there in the very situation, the very emotional state, or with the very object of thought (*18*). The embodiment of anger might involve tension in muscles used to strike, the enervation of certain facial muscles to form a scowl, and even the rise in diastolic blood pressure and in peripheral resistance, for example. The concept of reenactment and related concepts such as simulation, resonance, and emulation are widely accepted in theories of embodied cognition, but many different mechanistic neural accounts of it have been proposed (*19*). One promising possibility is that simulation is supported by specialized "mirror neurons" or even an entire "mirror neuron system," which maps the correspondences between the observed and performed actions. However, there is much disagreement about the exact location of the mirror neurons, whether these neurons actually constitute a "system" (in the sense of interconnected elements), and whether there actually are specialized neurons dedicated to mirroring (or whether regular neurons can simply perform a mirroring function). Some of the original work on mirror neurons in monkeys emphasized a distinctive role of neurons located in the inferior parietal and inferior frontal cortex, which discharge both when a monkey performs an action and when it observes another individual's action (*20*). The implications of this work

were quickly extended to humans. Some scientists argue that humans have a dedicated "mirror neuron area," located around the Broadmann's Area 44 (the human homolog of the monkey F5 region). This mirror neuron area may compute complex operations, such as mapping the correspondence between self and others or differentiating between goal-oriented versus nonintentional actions (*20*). But more questions about an architecture for embodied cognition have been raised than have been answered. The specifics of the underlying architecture will be one of the defining projects for neuroscience and neurophysiology in the coming years.

Perceiving Emotion

One hypothesis regarding the application of theories of embodied cognition to emotion is that the perception of emotional meaning—recognizing a facial expression of emotion or the words "snarling bear"—involves the embodiment of the implied emotion (*21*). There is now substantial empirical support for this hypothesis. Neuroimaging studies have revealed that recognizing a facial expression of emotion in another person and experiencing that emotion oneself involve overlapping neural circuits. In an illustrative study, researchers had participants inhale odors that generated feelings of disgust (*22*). The same participants then watched videos of other individuals expressing disgust. Results showed that areas of the anterior insula and, to some extent, the anterior cingulate cortex were activated both when individuals observed disgust in others and when they experienced disgust themselves [related findings are reported in (*23*, *24*)].

Similarly, behavioral studies demonstrate that emotional expressions and gestures are visibly imitated by observers and that this imitation is accompanied by self-reports of the associated emotional state (*25*). Theories of embodied cognition provide a theoretical account of why this is so: The imitation of other individuals' emotional expressions is part of the bodily reenactment of the experience of the other's state. When emotional imitation goes smoothly, there is a strong foundation for empathy (*26*) and, therefore, even good marriages. Mimicking the facial expressions of your partner is good for your relationship, even if this means that you will grow to resemble each other because you repeatedly use the same facial muscles, as the findings of one study suggest (*27*). In contrast, there is evidence that relates failures in processes of emotional imitation, such as those which occur in autism, with substantial problems in social interaction (*28*).

One important implication of this type of emotional resonance across individuals is its probable role in observational learning. In observational learning, the positive or negative consequences of a given behavior are learned by watching another individual experience these consequences. A recent functional magnetic resonance imaging study revealed similar changes in brain activity of a female participant when painful stimulation was applied to her own hand and to her partner's hand (*29*). A related study used single-cell recording and found activation of pain-related neurons when a painful stimulus was applied to the participant's own hand and also when the patient watched the painful stimulus applied to the experimenter's hand (*30*). This suggests that observational learning is supported by a reenactment of the emotional experience of the model in the observer. Although a direct test of such a claim is required, the same mechanism should underlie instructed learning. In instructed learning, neither the self nor another person ever experiences pain or pleasure. Rather, learning occurs through the transmission of language. When children learn not to put their fingers in electrical outlets or to carelessly run into the street, their behavior is guided by verbal instruction, not direct experience. They must, therefore, be able to reexperience an emotion when that emotional consequence is described in language. Already published comparisons of amygdala activation during conditioned, observational, and instructed fear-learning in humans are consistent with just such a view (*31*). The findings suggest that the emotional processes that support all three types of learning share important similarities.

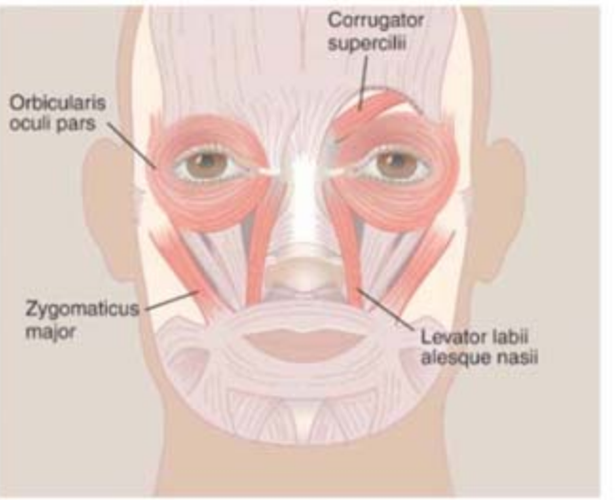

Fig. 3. The muscles associated with the facial expressions measured in recent work are shown. The orbicularis oculi and zygomaticus are activated to produce a smile, the corrugator is activated during frowning in anger, and the levator is used to produce the grimace of disgust.

Thinking About Emotion

In my own laboratory, we have demonstrated that using emotional information stored in memory involves embodiment (*32*). In one study, experimental participants made judgments (they provided a "yes" or "no" response) about whether words referring to concrete objects (e.g., "baby," "slug") were associated with an emotion. The objects had been rated by other individuals as being strongly associated with the emotions of joy, disgust, anger, or no particular emotion. During the task, the activation of four facial muscles (Fig. 3) was recorded with a technique called electromyographic recording. In another study, the same method was followed but the words now referred to abstract concepts; they were adjectives that denoted affective states and conditions (e.g., "joyful," "enraged").

Results of both studies showed that, in making their judgments, individuals embodied the relevant, discrete emotion as indicated by their facial expressions. The findings indicate that in the very brief time it took participants to decide that a "slug" was related to an emotion (less than 3 s), they expressed disgust on their faces. They appeared to make their judgments on the basis of the embodiment of the referent (objects for the first study and emotional states for the second). Further support for such a conclusion comes from the results of a second condition of each study. In fact, the experimenter instructed half of the participants to make a different judgment about the words. Those participants indicated ("yes" or "no") whether the words were written in capital letters. In order to make such judgments, these participants would not have to embody the emotional meaning of the words; indeed, findings revealed that these participants showed no systematic activation of the facial musculature whatsoever. The point that embodiment does not occur when the information can be processed on the basis of association or perceptual features has been made in other research as well (*33*, *34*).

Further evidence of the embodiment of emotional concepts was also obtained in extensions of research on the costs of switching processing between sensory modalities to the area of emotion. Researchers have shown that shifting from processing in one modality to another involves temporal processing costs (*35*): Individuals take longer to judge the location of a visual stimulus after having just detected the location of an auditory one, for example, than if both stimuli arrive to the same modality. For the present concerns, it is of interest that similar "switching costs" are also found when participants engage in conceptual tasks: Individuals are slower to say that typical instances of object categories have certain features if those features are processed in different modalities (*36*). They are slower to verify that a "bomb" can be "loud" when they have just confirmed that a "lemon" can be "tart" than compared to when, for example, they have just confirmed that "leaves" can be "rustling." This provides support for the general assertion made by theories of embodied cognition that individuals simulate objects in

the relevant modalities when they use them in thought and language.

Vermeulen and colleagues (*37*) examined switching costs in verifying properties of positive and negative concepts such as "triumph" and "victim." Properties of these concepts were taken from vision, audition, and the affective system. Parallel to switching costs observed for neutral concepts, the study showed that, for positive and negative concepts, verifying properties from different modalities produced costs such that reaction times were longer and error rates were higher than if no modality switching was required. This effect was observed when participants had to switch from the affective system to sensory modalities and vice versa. In other words, participants were less efficient in verifying that a "victim" can be "stricken" if the previous trial involved verifying that a "spider" can be "black" than they were if that previous trial involved verifying that an "orphan" can be "hopeless." And participants were less efficient in verifying that a "spider" can be "black" when that trial was preceded by the judgment that an "orphan" can be "hopeless" than if preceded by the judgment that a "wound" can be "open." This provides evidence that affective properties of concepts are simulated in the emotional system when the properties are the subject of active thought.

Comprehending Emotional Language

Developments in theories of embodied cognition to account for language make the claim that language comprehension relies in part on embodied conceptualizations of the situations that language describes (*38*). The first step in language comprehension, then, is to index words or phrases to embodied states that refer to these objects. Next, the observer simulates possible interactions with the objects. Finally, the message is understood when a coherent set of actions is created.

Some evidence in support of such an account of understanding emotional language was published almost 20 years ago, though no fully developed model was available at the time to interpret the findings. In the study, some participants held a pencil between their front teeth while performing a laboratory task that involved rating the funniness of different cartoons (*39*). Holding the pen in the mouth this way covertly led the individuals to smile. Other participants were instructed to hold a pencil between their lips, without touching the pencil with their teeth, and this prevented them from smiling (Fig. 1). Results revealed that, as suggested in the thought problem that began this article, individuals who were led to smile evaluated the cartoons as funnier than did participants whose smiles were blocked. It appeared that those individuals who were smiling somehow "got" the comic meaning of the cartoons better or easier than did the individuals who were prevented from smiling.

More evidence for simulation of emotions in sentence comprehension is now available (*40*). The reasoning that motivated the research was that if the comprehension of sentences with emotional meaning requires the partial reenactment of emotional bodily states, then reenactment of congruent (or incongruent) emotions should facilitate (or inhibit) language comprehension. Participants had to judge whether the sentences described a pleasant or an unpleasant event, while holding a pen between the teeth (again, to induce smiling) or between the lips (to inhibit smiling). Reading times for understanding sentences describing pleasant events were faster when participants were smiling than times when participants were prevented from smiling. Sentences that described unpleasant events were understood faster when participants were prevented from smiling than when they were smiling. The same effect was observed in a second experiment in which participants had to evaluate whether the sentences were easy or hard to understand.

Conclusions

Early critics of theories of embodied cognition argued that bodily feedback is too undifferentiated and too slow to represent emotional experience (*41*). In fact, the motor system alone can support extremely subtle distinctions. But, more importantly, recent theories of embodied cognition avoid such criticisms by focusing on the brain's modality-specific systems, not only on muscles and viscera. The circuits in modality-specific brain areas are fast, refined, and able to flexibly process a large number of states. These states can be reactivated without their output being observable in overt behavior. This account is ripe, therefore, to generate research that can further the understanding of learning, language comprehension, psychotherapeutic techniques, and attitudes and prejudice, just to name a few psychological phenomena. These days, those few seem to be pretty important.

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Sound Production in the Clownfish *Amphiprion clarkii*

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Although clownfish sounds were recorded as early as 1930 (*1*), the mechanism of sound production has remained obscure. Yet, clownfish are prolific "singers" that produce a wide variety of sounds, described as "chirps" and "pops" in both reproductive and agonistic behavioral contexts (*2*). Here, we describe the sonic mechanism of the clownfish *Amphiprion clarkii*.

We studied sounds (from three males and one female) directed toward conspecifics that approach their sea-anemone hosts. Sound recordings, synchronized with high-speed video (500 fps) coupled ($n = 9$) or not ($n = 22$) with an x-ray system, allowed us to quantify movements of skeletal elements (*3*).

A. clarkii sounds (Fig. 1) are produced in trains of one to eight pulses (means for duration, 26 ms; pulse period, 35 ms; and energy, between about 450 to 800 Hz). These parameters do not correspond with typical stridulatory mechanisms (*4*) and have higher frequency components than swimbladder sounds driven as a forced response to sonic muscle contraction (*5*).

Sounds ($n = 14$) were typically accompanied by rapid (<30 ms) movements that include an elevation of the head, lowering of the hyoid bar and anterior part of the branchial basket, a backward movement of the pectoral girdle, and lastly a closing of the lower jaws (movie S1). Synchronization of sound pulses with the video images indicates that sound is produced when the hyoid apparatus is rapidly lowered (23.8 m/s^2, $n = 50$ frames) and the mouth simultaneously closed (Fig. 1).

Manipulations of specimens show that low-amplitude elevations of the skull lower the jaws and branchial basket, a phenomenon well known in fish feeding (*3*, *6*). Rather than accentuating this movement, a higher-amplitude elevation of the head actually forces the mouth to close by a previously unknown mechanism.

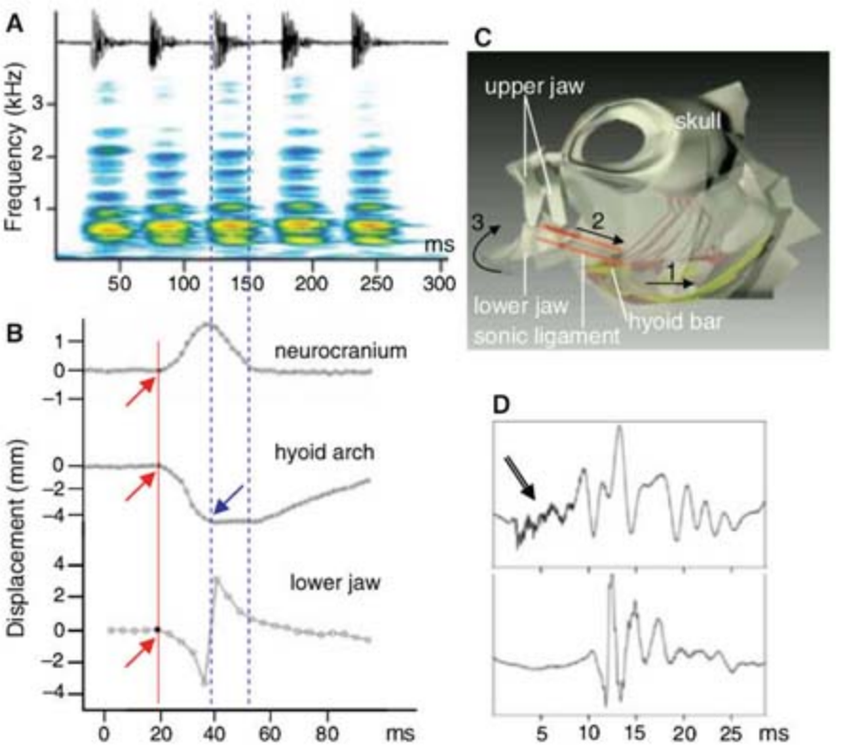

Fig. 1. Sound production in *A. clarkii*. (**A**) Oscillogram and sonagram of a train of pulses. (**B**) Graphs of the movements of different skeletal elements during sound production. The red line indicates the beginning of the sonic movement; the blue arrow, the pulse onset; and double dotted lines, the sound duration. (**C**) Schematic representation of the sound-producing mechanism, illustrating the relative movement of skeletal components. Lowering the hyoid bar (1) stretches the sonic ligament (2), and the jaw closes the mouth (3) by rotating around the mandible articulation on the quadrate. See also movies S1 and S2. (**D**) Oscillogram of a pulse. Top selection is sound from an intact fish; bottom selection, sound from the same fish after the jaw teeth were cut. The bottom pulse is shorter and deprived of the high-frequency onset (arrow).

Dissections reveal that an unusual sonic ligament is responsible for the rapid lower jaw elevation. The ligament joins the hyoid bar (ceratohyal) to the internal part of the mandible (coronoid process of the articulo-angular) and can be compared to a drawbridge (movie S2). The ligament, acting as a cord, forces the mandible to turn around its articulation during the lowering of the hyoid bar, forcing the mouth to close (Fig. 1). Sound results from the collisions of the jaw teeth, transferring energy to the jaws that are presumably the sound radiator. Transecting the right and left sonic ligaments muted the fish, supporting our hypothesis. Furthermore, cutting upper and lower jaw teeth resulted in shorter sounds (23 versus 48 ms, $P < 0.0001$, $n = 38$ pulses) without the typical low-amplitude high-frequency onset. This result indicates that intact sounds start with teeth collisions (Fig. 1).

Species-specific sounds are produced by all 27 *Amphiprion* species and appear to be supported at least by interspecific variation in teeth shape. The sonic ligament is present in other members of the damselfish family (*7*), many of whom produce communication sounds (*8*). The homologous ligament mechanism is likely involved in sound production throughout this large family and represents a novel skeletal adaptation for a new behavioral function. This functional movement seems to be an exaptation of the feeding mechanism.

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Supporting Online Material

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Movies S1 and S2

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Bose-Einstein Condensation of Microcavity Polaritons in a Trap

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We have created polaritons in a harmonic potential trap analogous to atoms in optical traps. The trap can be loaded by creating polaritons 50 micrometers from its center that are allowed to drift into the trap. When the density of polaritons exceeds a critical threshold, we observe a number of signatures of Bose-Einstein condensation: spectral and spatial narrowing, a peak at zero momentum in the momentum distribution, first-order coherence, and spontaneous linear polarization of the light emission. The polaritons, which are eigenstates of the light-matter system in a microcavity, remain in the strong coupling regime while going through this dynamical phase transition.

Work in several promising systems has pointed to Bose-Einstein condensation (BEC) of new types of quasiparticles in solids (*1*): a state that can be called a "coherent solid." In such systems, the electronic degrees of freedom of the solid can undergo a phase transition to spontaneous coherence that is analogous in some ways to superconductivity but that also emits coherent radiation.

Several recent experiments (*2*–*5*) have indicated spontaneous coherence in exciton-polariton gases in various two-dimensional (2D) semiconductor microcavity structures. In each of these experiments, a laser was focused on the sample, with polaritons generated at high density at the laser spot. The coherent effects were seen only at the same place where the laser excited the samples and only during the time when the laser was on. Although it was argued with reasonable justification (*1*) that the coherent state created in these experiments had many of the characteristics of a BEC, a basic question has remained: Because the coherent emission occurs only in the region excited by the laser, is it possible that the coherent effects are essentially the same as a nonlinear amplification of the laser itself? Also, because the polaritons were not created in a confining geometry in those experiments, the ground state of the system was poorly defined: The polaritons could freely diffuse away from the excitation region or fall into local minima created by disorder.

We report the demonstration of a spatial trap for the polaritons in the plane of their motion. This trap is well approximated by a harmonic potential at its minimum, allowing confinement of the polaritons at low temperature. Confinement of the particles in a macroscopic trap is known (*6*) to make BEC allowable in two dimensions with a condensate of finite size, similar to a condensate in a 3D trap (*7*). The trap also produces an evaporative cooling effect for the polaritons. Most importantly, we can generate the polaritons with a laser that is focused far from the center of the trap and watch them accumulate in the bottom of the trap where there is no laser excitation. In a trap, the polaritons exhibit the effects associated with spontaneous Bose coherence seen in previous experiments (*2*). The fact that we can see these direct evidences of spontaneous coherence of polaritons in a GaAs-based microcavity structure improves accessibility, because of the growth and fabrication issues for the II-VI semiconductor structures used in previous experiments (*2*).

It is by now well established (*8*) that exciton-polaritons in microcavities act as a gas of weakly interacting bosons with extremely light mass (measured as 7×10^{-5} of the vacuum electron mass in our experiments), which implies very high critical temperature for Bose coherent effects. An exciton-polariton is a linear combination of a cavity photon, which has extremely light effective mass in the 2D plane of the cavity, and a quantum-well exciton. Coupling occurs between the photon states and the exciton states because the excitons are generated and decay by a dipole-allowed interband electronic transition. Cavity photons by themselves are essentially noninteracting, but polaritons interact with each other via a short-range interaction due to their exciton component (*9*).

Trapping polaritons. Our structures are essentially identical in design with those used in earlier work (*3*, *4*). Three groups of four identical 70 Å quantum wells are located at the antinodes of a cavity photon mode to maximize the coupling of the exciton and photon states. In earlier work (*4*), it was shown that the lasing transition in these structures is distinct from the onset of coherence in the polariton states, because two distinctly different threshold behaviors could be observed. However, those experiments did not use trapping of the excitons, and they also used very different excitation conditions, namely, an intense pulsed laser with photon energy resonant with the lowest polariton states and at a large incident angle.

Exciton-polaritons in these structures can be created by any mechanism that creates electrons and holes in the quantum wells. In the present work, we create free electrons and holes by pumping with a low-intensity circularly polarized beam from a Ti:Sapphire laser, with photon energy that is high above the lowest polariton states (excess energy = 129 meV), at the first reflectivity minimum above the cavity stop band. This process acts as an incoherent source of

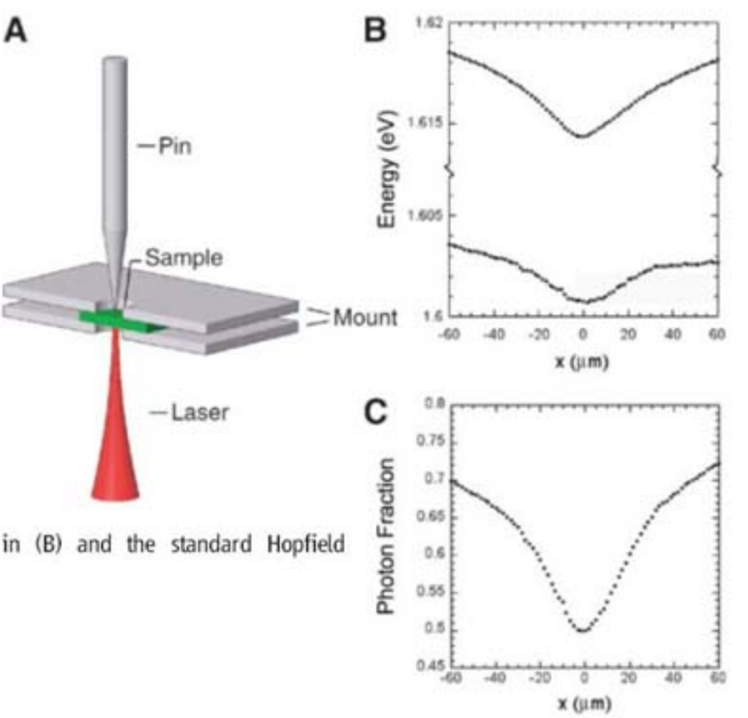

Fig. 1. (**A**) Stress geometry for the microcavity structure. (**B**) Upper and lower polariton energies (top and bottom traces, respectively), deduced from photoluminescence and reflectivity spectra at very low excitation density and low lattice temperature (T = 4 K), when a force of 0.975 N on the pin stressor is applied to the sample. (**C**) Photon fraction of the lower polariton branch as a function of position in the trap, calculated from the polariton energies shown in (B) and the standard Hopfield coefficients.

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polaritons, because the generated electrons and holes must emit many phonons to drop down into the polariton states at the bottom of the band. The pump laser was directed to the sample at an incident angle of $\theta = 17°$; unlike many earlier "magic angle" experiments (*10*–*12*), the angle of the incident beam is not important in our experiments because the photon energy is so far above the polariton states of interest. For all these experiments, the sample was held in helium vapor at temperature $T = 4.2$ K.

Polaritons decay by turning into photons, which exit the cavity. These emitted photons are our primary way of observing the behavior of the polaritons. The in-plane component of the momentum must be conserved in the conversion of polaritons to external photons, which implies that the angle of emission of a detected photon tells us the in-plane momentum of the polariton at the moment of decay. By recording the spectrum of the emitted light as a function of emission angle, we therefore have a complete measurement of the momentum and energy distribution of the polaritons.

The trapping method that we use has been reported earlier (*13*) and is based on a similar method developed for quantum-well excitons (*14*, *15*). In these microcavity structures, the thicknesses of the epitaxial layers vary across the wafer so that the intrinsic detuning of the exciton and cavity photon states varies continuously. For the stress trapping experiments, we choose a piece of the wafer where the cavity is initially negatively detuned, with $\delta \approx -10$ meV ($\delta = E_{cav} - E_{ex}$, where E_{cav} is the cavity photon energy and E_{ex} is the bare exciton energy). As illustrated (Fig. 1A), a force is applied with a rounded-tip pin (tip radius = ~50 μm) on the back side of the substrate, which is ~100 μm thick. The stress shifts the exciton states while the cavity photon energy is left essentially unchanged. Directly under the stressor, the lower polariton branch has an energy minimum (Fig. 1B), which can be well fit by a harmonic potential $U = [1/2]\,\gamma r^2$ (where r is the distance from the center of the trap and $\gamma = 480$ eV/cm^2) that corresponds to a quantum level spacing in the harmonic potential of $\hbar\omega_0 = 0.066$ meV (where $\hbar$ is Planck's constant h divided by 2π and $\omega_0 = \sqrt{\gamma/m}$ is the natural frequency, with effective mass m), which is much less than $k_B T$ (where k_B is Boltzmann's constant), so that the continuum approximation for the polariton states in the trap is valid.

The shift of the exciton states with stress also affects the coupling of the exciton states and cavity photon states. In the center of the trap, the cavity photon states and the exciton states are strongly coupled; however, far from the center, the lowest polariton states are almost purely photon-like. Figure 1C shows the photon fraction of the lower polariton branch, deduced from the data of Fig. 1B by means of the standard Hopfield coefficients (*8*). This means that the trap also causes evaporative cooling, because the lifetime of the polaritons at high energy (far from the center) is shorter than the lifetime of those at the energy minimum (in the center). Of course, this effect will work only if the polaritons have diffusion lengths long enough to move through the whole trap. This is the case in our experiments, where in some cases the polaritons move more than 50 μm. In principle, this effect can be increased by the use of larger stress to positively detune the cavity at the center of the trap so that the polaritons are more than 50% exciton-like at the center and become completely photon-like far from the center.

Figure 2 shows a series of images in which the position of the laser spot that creates the polaritons is scanned across the well. The vertical axis of this figure indicates the energy of the polaritons, whereas the horizontal axis gives the spatial position in the plane of their motion. When created by the laser on one side, the polaritons flow down into the trap; when created by the laser on the other side, they flow in the opposite direction into the trap. For these experiments, the laser was quasi–continuous wave (cw), with a 2.4% duty cycle at 1 kHz. The low duty cycle turns out to be essential to see long-range motion of the polaritons, because it reduces the overall heating of the sample; heating of the lattice leads to a very low diffusion constant for the polaritons.

Signatures of condensation. Under these conditions, we observe several signatures of spontaneous coherence of polaritons. We observe a critical excitation density threshold for nonlinear gain (Fig. 3A), which is similar to that observed under a wide variety of conditions for polaritons in microcavities (*2*, *4*). Below this threshold, the spectral width of the photoluminescence emitted normal to the surface broadens with increasing density; however, at the threshold, the width of the photoluminescence spectrum drops sharply. At the same time, we observe spatial contraction (Fig. 3B) of the polariton cloud by a factor of three, down to the limit of our spatial imaging resolution (8 μm). [Spatial contraction of the polariton cloud is shown in images in the supporting online

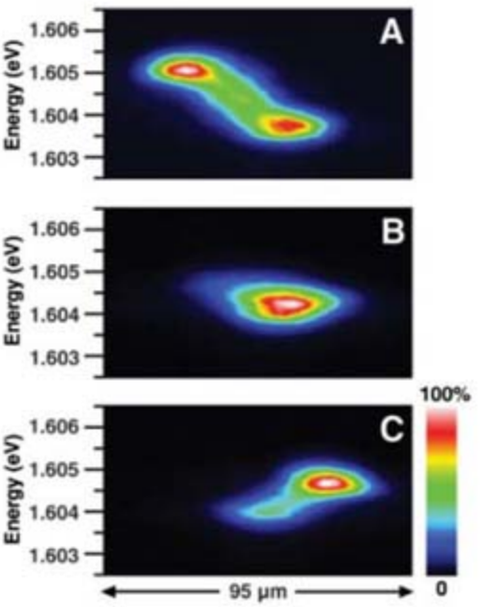

Fig. 2. Spatially resolved spectra of the light emission (external angle $\theta = 0 \pm 1.0°$) from polaritons in the microcavity structure for three different positions of the laser. The polaritons are created on the left and flow to the right in (**A**), are created in the trap in (**B**), and are created on the right and flow to the left in (**C**). The average laser power was 2.4 mW for quasi-cw excitation with 2.4% duty cycle at 1 kHz.

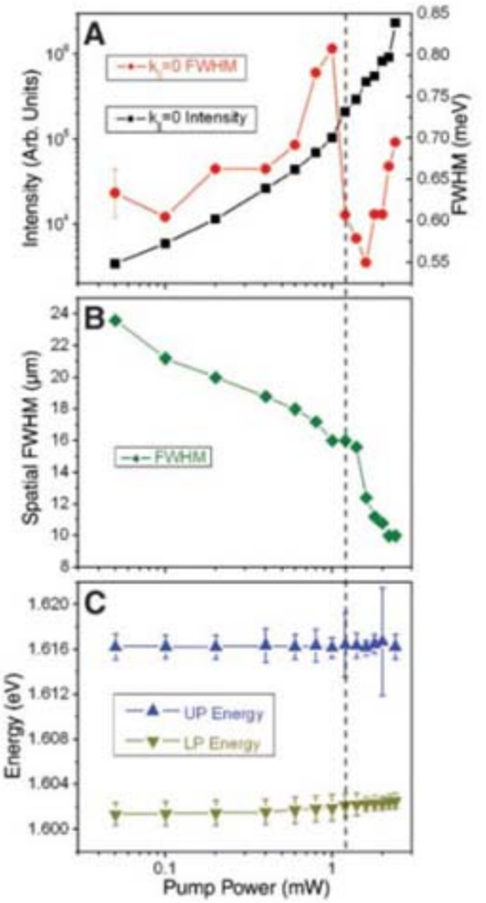

Fig. 3. Data for polaritons in the center of the trap when the laser creates the polaritons on the side of the trap, far from the center, similar to the conditions of Fig. 2. (**A**) Black squares indicate total photoluminescence intensity at $k_{\parallel} = 0$ (external angle $\theta = 0 \pm 1.0°$) as a function of average excitation power, for quasi-cw excitation with 2.4% duty cycle. Red circles indicate full width at half maximum (FWHM) of the emission spectrum at $k_{\parallel} = 0$ under the same conditions, which was collected from an 8-μm spot in the center of the trap. (**B**) FWHM of the spatial profile of the photoluminescence collected for external angle $\theta = 0 \pm 5.2°$ from the center of the trap under the same conditions as in (A). (**C**) Upper and lower polariton energies deduced from photoluminescence (lower polariton) and reflectivity (upper polariton) under the same conditions as in (A). The vertical dashed line through the three panels is an indicator of the critical threshold. The error bars in (A) represent the instrumental resolution, and the error bars in (C) are the 1σ uncertainty of the best fit to the data.

material (SOM). The spatial profiles are in marked contrast to previous experiments (*2*) that showed a very irregular pattern of the coherent emission, presumably determined by the local disorder potential.] Spatial contraction is also a telltale sign for condensation in a trap because the condensate seeks the ground state of the system, which (in the case of a trapped gas) is a compact state at the bottom of the trap. Below the critical density, in the normal state, the size of the cloud is determined by a steady-state balance of the pumping by the exciting laser and thermal diffusion; above the critical density, the size of the cloud is given by the size of the ground state of the many-particle system. If interactions are neglected, the standard solution of a harmonic oscillator gives a ground-state wave function with extent $a = \sqrt{\hbar/m\omega_0}$, which for our parameters is 3.8 μm. In the presence of particle-particle repulsion, the size of the ground state will expand (*16*), but its size is still expected to be small as compared to the size of the cloud of thermal particles. This is a major difference between experiments with and without traps: In a translationally invariant geometry, a superfluid will flow outward; whereas, in a trap, it will flow inward. Over the whole range of polariton density, the system remains in the strong coupling regime, as evidenced by the relatively small measured shifts of the lower and upper polariton lines (Fig. 3C).

In addition to these effects, a signature for BEC is the momentum distribution of the particles, which can be measured for polaritons by resolving the angular distribution of the photoemission. Figure 4 shows a series of angle-resolved spectra under the same conditions as in Fig. 3, but with the laser aimed at the center of the trap to give a clearer signal (when the laser is aimed at the side of the trap, the emission from the side of the trap overlaps the signal from the center in the angle-resolved data). There is a dramatic narrowing of both the in-plane momentum $k_\parallel$ and energy of the polaritons above the critical threshold, while the blue shift due to interactions of the polaritons remains very low. The contraction in momentum space that is simultaneous with contraction in real space (Fig. 3B) does not contradict the uncertainty principle because both the spatial cloud size and the momentum distribution are determined by thermal scattering when the polariton gas is in the normal state, below the critical density threshold. Therefore, the total uncertainty in the normal state $\Delta k_\parallel \Delta x$ (where $\Delta k_\parallel$ is the uncertainty in the in-plane momentum and Δx is the uncertainty in the in-plane position) is much larger than unity. The spatial size of the condensate does imply a minimum width of the momentum peak at $k_\parallel = 0$, which is consistent with our data within our spatial and spectral resolution limits.

Figure 4E shows the relative number of polaritons per $k_\parallel$ state deduced from the same data. The photoluminescence intensity data have been converted to an occupation number with the use of the polariton lifetime deduced from the Hopfield coefficient as a function of $k_\parallel$, as in previous works (*2*, *5*). The energy for each $k_\parallel$ is determined by the maximum of the measured spectrum at each $k_\parallel$, in the same way as in (*2*). Far below the critical density threshold, the polariton distribution is completely nonthermal. Just below the critical density threshold, the distribution is well fit by a Maxwell-Boltzmann distribution $N(E_k) \propto e^{-E_k/k_B T}$ [where E_k is the particle energy, and $N(E_k)$ is the number of particles per state at that energy], which corresponds to a straight line on this plot. Above the critical threshold, there is a sharp increase in the number of polaritons near $k_\parallel = 0$.

The high temperature of the Maxwell-Boltzmann fit below the critical density, which is mirrored in the high-energy tails of the higher-density $N(E_k)$, indicates that the polariton gas is not completely thermalized. As shown in recent theoretical works (*17*–*19*), the lack of complete equilibrium does not prevent the polariton gas from undergoing a phase transition to spontaneous coherence. The buildup of the particles at $k_\parallel = 0$ is truly an effect of the Bose statistics, but the entire range of energy cannot be fit to an equilibrium Bose-Einstein distribution because the high–kinetic energy particles ($E_k > \sim 1.5$ meV) are constantly heated by hot polaritons generated by the laser. This is also true of the occupation-number data of (*2*). Steady-state quasiequilibrium theory (*17*–*19*) predicts a bimodal distribution function $N(E_k)$ [with a peak at $k_\parallel = 0$ like that seen in Fig. 4E, which corresponds to a condensate] even when the system is not in complete equilibrium.

Similar to (*2*), we also see spontaneous linear polarization above the critical density threshold (Fig. 5). Below the threshold, the light emission is essentially unpolarized, which is not surprising because the pump light is circularly polarized and the generated carriers must emit numerous phonons. Above the critical threshold, the light becomes linearly polarized. We checked that this polarization is not related to the excitation polarization or to the detection system by rotating the sample relative to the system. We found that the linear polarization follows the sample orientation and is nearly aligned with the [110] axis of the crystal, as in the CdTe experiments (*2*). The polarization angle also appears to depend weakly on the applied stress. Linear polarization has been predicted (*20*) to be a direct result of spontaneous symmetry breaking in the polariton condensate system; more recent theoretical work has shown that pinning along a crystal symmetry direction is expected (*21*). In general, when there is a condensate, any small term in the Hamiltonian that breaks the degeneracy of the ground state will cause the condensate to jump into the lowest energy state.

Direct measure of coherence onset. Under slightly different conditions, we can also see direct evidence of coherence in the first-order correlation of the photoluminescence, which is also seen in the work in CdTe structures (*2*). For

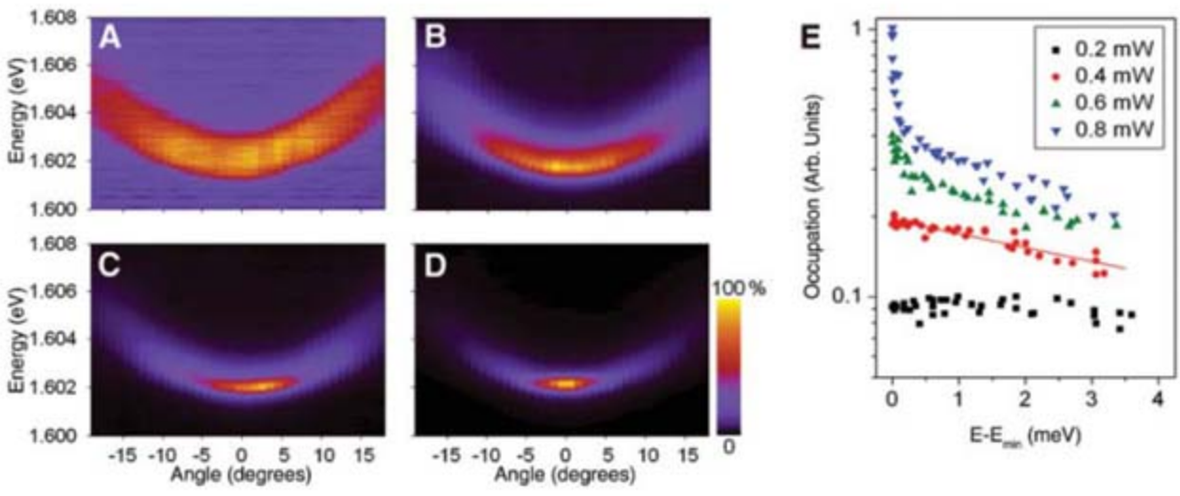

Fig. 4. Momentum distribution of the polaritons as measured by angle-resolved photoluminescence intensity for four different powers (under the same conditions as in Fig. 3, but with the laser aimed at the center of the trap). Angle-resolved spectra for (**A**) 0.05-mW pump power (far below the threshold density), (**B**) 0.4-mW pump power (just below the threshold), (**C**) 0.6-mW pump power (at the threshold), and (**D**) 0.8-mW pump power (above the threshold). The false-color scale is linear, with yellow and black indicating high and low values, respectively. (**E**) Number of polaritons per k state, deduced from the data of (A) to (D). The straight line is a fit to a Maxwell-Boltzmann distribution with $T = 97$ K. $E - E_{min}$ is the peak energy of the luminescence at each angle, relative to the minimum energy (at $k_\parallel = 0$).

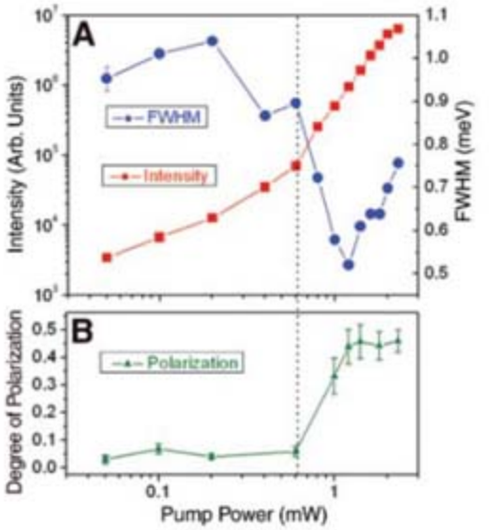

Fig. 5. (**A**) Red squares indicate total photoluminescence intensity at $k_{||} = 0$ (external angle $\theta = 0 \pm 1.0°$) as a function of average excitation power, for the same conditions as in Fig. 4. Blue circles indicate FWHM of the emission spectrum at $k_{||} = 0$ under the same conditions, collected from an 8-μm spot in the center of the trap. (**B**) Degree of polarization $[(I_{max} - I_{min})/(I_{max} + I_{min})]$ under the same conditions as in (A).The vertical dashed line is an indicator of the critical threshold. The error bars in (A) represent the instrumental resolution, and the error bars in (B) are the 1σ uncertainty of the best fit to the data.

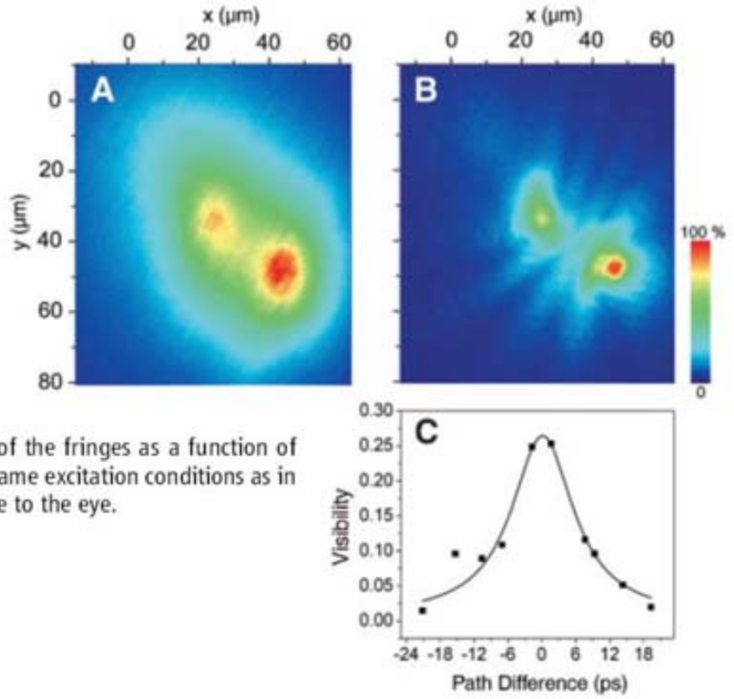

Fig. 6. False-color interference pattern created by sending the light emission through a slightly misaligned Michelson interferometer, with the cw pump laser aimed at the center of the trap. Laser power is shown below and above threshold in (**A**) and (**B**), respectively; cw average power is 37 mW in (A) and 73 mW in (B). Total time delay of one path relative to the other was 1.56 ps. (**C**) Visibility of the fringes as a function of path difference under the same excitation conditions as in (B). The solid line is a guide to the eye.

these measurements, we used a cw laser in order to get the maximum luminescence intensity from the sample. The average power of the laser is much higher than in the low-duty-cycle experiments discussed above, and the diffusion constant is much lower than in the low-duty-cycle experiments. However, when the laser is aimed at the center of the trap, we see essentially the same behavior—spectral narrowing, beamlike emission in a narrow range of angle corresponding to polaritons with $k_{||} \cong 0$, and spontaneous linear polarization—as that seen in the experiments with low duty cycle for the pump laser.

Figure 6 shows images produced by sending the spatially resolved photoluminescence through two arms of a Michelson interferometer, when the interferometer is slightly misaligned to create a double image [in which the left side of the image from one arm overlaps with the right side of the image from the other arm (single images of the spot under these conditions are shown in the SOM)]. In this way, we detect the spatial correlation across the length of the polariton cloud, including the low-density tail, which extends 20 μm from the center. Below the critical excitation density threshold, we cannot see any interference fringes for any path difference of the two arms of the interferometer (Fig. 6A). Above the critical density, fringes appear (Fig. 6B). Figure 6C shows the visibility of the fringes, $(I_{max} - I_{min})/(I_{max} + I_{min})$, where I_{max} and I_{min} are the maximum and minimum intensity, respectively, as the path length is varied under the same excitation conditions as in panel B. The visibility is never 100%, which is consistent with recent theoretical predictions (*22*) that the condensate fraction of the polariton gas should be less than 50%. The coherence time increases from less than 1 ps below the critical threshold to 8 to 10 ps above the critical threshold, which is longer than the nominal lifetime of the polaritons in these structures of around 4 ps (*4*).

Concluding remarks. The dramatic transition of the system to a linearly polarized, compact, coherent, beamlike light source is consistent so far with the picture of quasiequilibrium BEC of exciton-polaritons. The ability to trap the polaritons allows us to observe many of these effects under conditions when the polaritons are confined in a region far from the laser generation point.

Although it may be hard to visualize polaritons, and although their lifetime is short, this system has all of the same essential features as those of atoms in traps. The polaritons act as a gas, moving through the semiconductor medium, and are trapped in a harmonic potential. The same basic theory of condensates and spontaneous coherence underlies both systems. In this case, the differences are that the system is truly two-dimensional and is in a quasiequilibrium steady state, with an incoherent pump.

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Regolith Migration and Sorting on Asteroid Itokawa

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High-resolution images of the surface of asteroid Itokawa from the Hayabusa mission reveal it to be covered with unconsolidated millimeter-sized and larger gravels. Locations and morphologic characteristics of this gravel indicate that Itokawa has experienced considerable vibrations, which have triggered global-scale granular processes in its dry, vacuum, microgravity environment. These processes likely include granular convection, landslide-like granular migrations, and particle sorting, resulting in the segregation of the fine gravels into areas of potential lows. Granular processes become major resurfacing processes because of Itokawa's small size, implying that they can occur on other small asteroids should those have regolith.

The degree to which small asteroids are covered by regolith (*1*) is an important unanswered question with implications for the evolution of these bodies. Formation of regolith on asteroids is different from that on the Moon (*2*) because of substantial differences in surface accelerations. Whereas repetitious impacts on the Moon form locally concentrated, size-sorted regolith, impact ejecta on an asteroid are ballistically spread over the entire surface to form globally continuous, generally uniform, and poorly sorted regolith with large fractions of escaping ejecta (*2*). However, the small (~300-m diameter) near-Earth asteroid Itokawa (*3*) has a considerable amount of regolith distributed nonuniformly. This poses the fundamental question of how the regolith has been segregated. Because Itokawa is by far the smallest asteroid ever studied at high resolution, previously unrecognized processes of regolith evolution may be active.

In November 2005, the Hayabusa spacecraft performed touchdown rehearsals, imaging navigation tests, and two touchdowns on Itokawa (*4*). These provided close-up images of Itokawa, mostly on the east side (fig. S1) at ranges below 2 km and down to 63 m, where image resolution was 6 mm per pixel (Figs. 1 to 3). Close-up images reveal the surface to be covered with unconsolidated gravels (*5*), which are typically piled on each other without being buried by fines (Figs. 1 to 3). These unconsolidated gravels commonly have the following two characteristics regardless of location: None of the smaller gravels in close-up images are isolated on top of boulders without being supported by other gravels (Figs. 1C and 2), and the position and orientation of gravels are apparently stable against local gravity (Figs. 1C, 2, and 3B). These give a strong indication that gravels on the surface of Itokawa were reallocated after their accumulation/deposition, implying that the surface has been subject to global vibrations. Vibrations are also suggested by the shapes of craters that are generally obscured on Itokawa (*6*) and often associated with partially disrupted rims (Fig. 1, A and D). These vibrations may have been caused by impact-induced seismic shaking (*7*, *8*), because a centimeter-sized impactor can globally induce seismic acceleration on Itokawa as large as its surface gravity (Fig. 4A). Other possible reasons for vibrations include tidal effects, thermally induced mechanical fluctuations, or low-speed collisions between the head and the body (*3*) due to a high spin rate of the asteroid in the past (*9*).

Grain sizes observed in close-up images range from centimeters to several tens of meters. The finest particles are centimeter-sized pebbles, whose concentrations are found in the Muses-C smooth terrain (Fig. 3A and fig. S1). Although powdery materials are thought to be created through impact processes (*10*–*12*), they might have been electrostatically levitated and removed by solar radiation pressure (*13*, *14*), had much higher ejection velocity after impacts to restrict their reaccumulations (*10*), or been segregated into the interior.

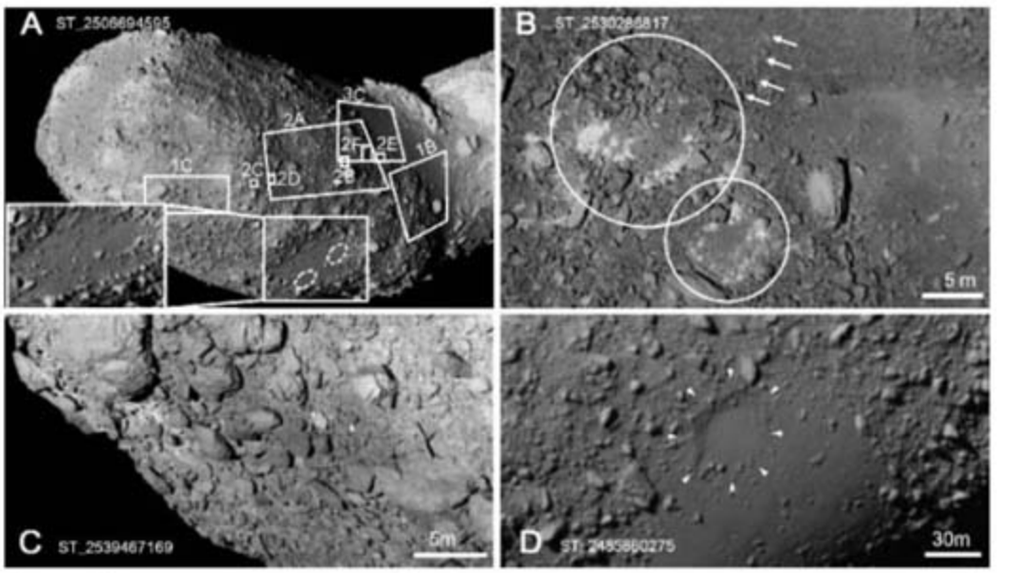

Fig. 1. (**A**) Locations of close-up images (number and letter of the figure where each image is shown). Inset shows the Uchinoura smooth terrain, which is likely formed by a single crater or a cluster of craters (dotted circles). Note the disrupted crater rims and flattened floors filled by fine gravels. (**B**) Piles of gravels with craterlike depressions (circles) (see fig. S2). Debris of a collapsed rim drained into the smooth terrain (arrows), which is a gravitational low. (**C**) Rounded boulders are sitting in stable orientations against local gravity. (**D**) A crater candidate in the Sagamihara smooth terrain with the disrupted rim (triangles) and the flat floor. In all images, numbers starting with "ST_" indicate their image frames. Upper portions of some images are obscured by the onboard polarizer (*6*).

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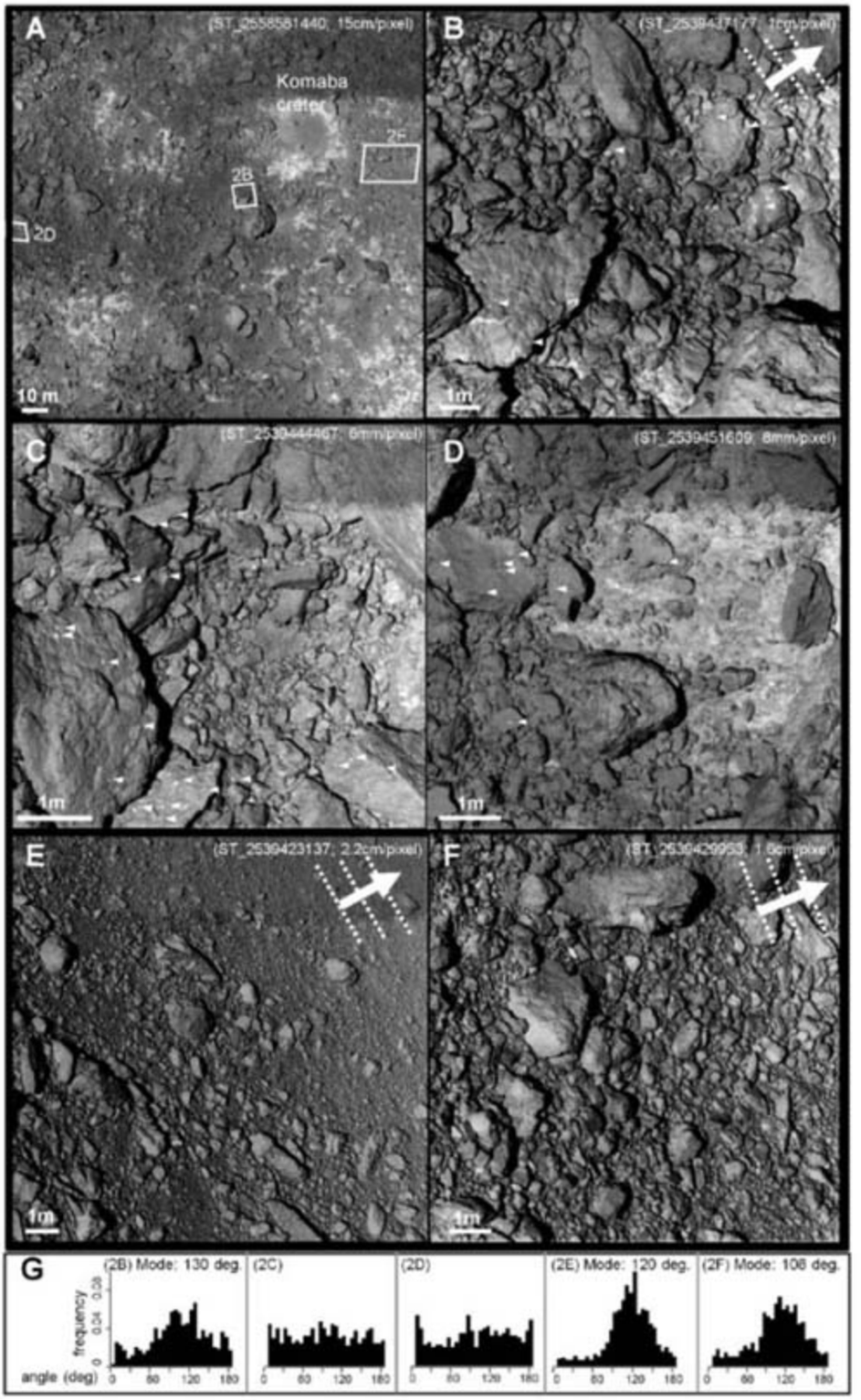

Fig. 2. (**A**) The rough terrain around the Komaba crater (Fig. 1A), showing locations of individual close-up images. (**B**) Gravels are weakly organized in the direction of the dotted lines. Bright dots (triangles) are observed on gravels of various sizes. (**C**) Larger gravels generally overlie smaller particles (potentially inverse grading). Some boulders have bright dots (triangles). (**D**) Close-up of the rough terrain with a brighter part exposed beneath the gravels. Some boulders have bright dots (triangles). (**E**) The boundary area between Muses-C and the rough terrain. Piles of gravel around boulders exist only in the uphill sides of the gravitational slopes (fig. S3). Alignments of boulders (dotted lines) indicate gravel migrations in the direction of the arrow. (**F**) The boundary area close to the Komaba crater showing clear gravel imbrication. (**G**) Frequency distributions of the angles (from horizontal) of the longest axis of gravels in images (B) to (F). Gravels larger than 100 pixels in each image [565, 897, 976, 396, and 426 gravels identified in (B), (C), (D), (E), and (F), respectively] are used to remove the sun-angle bias. Whereas gravel orientations of (C) and (D) are almost random, those of (B), (E), and (F), are clearly organized. The modes of the orientations are plotted as dotted lines. Organization of gravels (or imbrications) is often observed for terrestrial river-bed gravel, where the longest axes are preferentially oriented transverse to the gravel migration (arrows).

We identify three major smooth terrains on Itokawa, the Muses-C, Sagamihara, and Uchinoura regions (Fig. 3D and fig. S1). Although the high-resolution images of smooth terrains (Fig. 3A) were only obtained at one particular portion of the Muses-C region (Fig. 3C), the slight variations in the brightness, surface texture, and color (*6*) of the smooth terrains in distant images indicate that the pebbles observed in Fig. 3A likely cover the rest of the Muses-C region and other smooth terrains uniformly.

The smooth terrains have generally homogeneous and featureless appearances, with a very limited number of craters. The overall slopes of the smooth terrains are typically nonzero but <8°. Detailed observations of the high-resolution images of the Muses-C region provide the following important characteristics: Most of the larger gravels are not buried by pebbles, even at their margins; larger particles, such as cobbles, tend to form clusters (Fig. 3A); and the larger gravels are aligned with directions coincident with the local gravity slope (Fig. 3D). We interpret these as resulting from the substantial vibrations discussed above, because these characteristics are consistent with laboratory experiments in which granular materials show granular convection, typically caused by vertical vibrations (*15*–*17*). Granular convection causes continuous flows of particles sliding down from the top of a convection cell, whose slope angle is within the friction angles of particles (*18*, *19*). Thus, the low slope angles of smooth terrains likely indicate the low friction angles of pebbles, similar to those on Earth (*20*).

Smooth terrains are not randomly distributed on the surface of Itokawa; all of the smooth terrains are in areas of low gravitational plus rotational potential. Moreover, small local lows such as crater floors are commonly filled by smooth materials (Fig. 1, A and D). The locations of both poles match the apexes of domelike shapes in the smooth terrains, which is expected for a slowly rotating body because polar regions will in general be the stable settling point for loose material (*21*). Because the gravitational slopes (Fig. 3D) in the rough terrains are always toward the smooth terrains, the above observations suggest global processes that segregate and migrate the finest gravels to these low points.

Gravel migrations in rough terrains are evidenced by a range of morphological characteristics, as often observed in terrestrial landslide deposits, including imbrications of boulders (Fig. 2, B, E, and F), piles of gravel exclusively on the uphill sides of gravitational slopes (Fig. 2E and fig. S3), larger and often angular boulders with strong alignments (Figs. 2E and 3C), and similarly shaped boulders exhibiting jigsaw-fit textures (Figs. 2E and 3C). The direction of gravel migrations consistently matches with local gravitational slopes (Fig. 3D), supporting the view that migrations are gravity-induced.

Given the dry, vacuum environment on Itokawa, whose escape velocity varies between

10 and 20 cm/s, the migrations discussed above could result from gravel fluidization induced by vibrations (*15*). Vibration can play a major role in the evolution of Itokawa's regolith because Itokawa's small size can keep seismic energy high (Fig. 4A) and because any point on the asteroid is only a short distance from the source of vibration (*22*, *23*). These factors may help keep vibrations active for a relatively long time to support particle fluidization (*22*, *23*). Although the high porosity (~40%) (*24*) and the hypothesized rubble-pile structure (*3*) may substantially attenuate seismic energy, the estimated high restitution value for the Muses-C region (*4*) indicates relatively compacted regolith particles and suggests that seismic attenuation may not be as large. Vibrations might have segregated particles much finer than pebbles into the

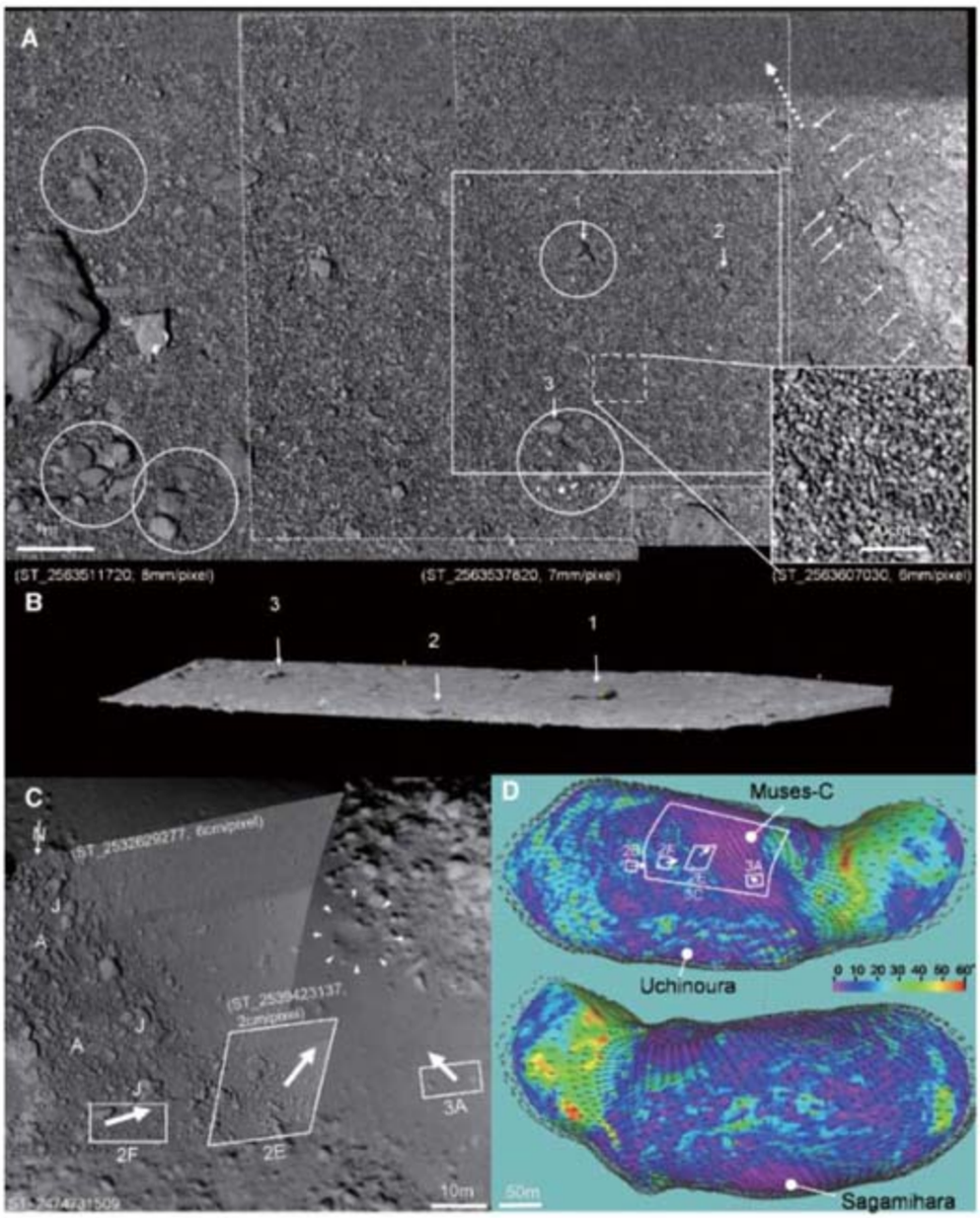

Fig. 3. (**A**) Mosaic of the highest-resolution images in the Muses-C region. The dotted area is overlapped by at least two images, which allows for detailed stereo analyses in (B). Circles indicate clusters of larger gravels. Alignment of cobbles (arrows) indicates the overall gravel migration along the direction of the dotted arrow. The white box shows the area graphically plotted in (B). Boulders with numbers are indicated in (B). (**B**) Three-dimensional model derived from the numerical stereo analyses with more than 11,000 control points. Viewed from the upper right side of (A). Note the flat, featureless surface and the boulders sitting on top of fines in gravitationally stable orientations, which suggests that these boulders are stranded by vibration-induced convections. (**C**) Muses-C and its boundary area. Directions of gravel migrations estimated from morphological characteristics are indicated by arrows. Alignments of boulders A and the jigsaw-fit structures J are identified. A craterlike depression (triangles) is apparently filled by fines. (**D**) The surface slopes (color) and their directions (triangles) computed by combining a polyhedral model of the Itokawa shape and rotation with a constant-density assumption. Note the global trend that the slopes are always toward the smooth terrains. The directions of gravel migrations derived from morphologic characteristics of deposits (arrows) match with those of local slope.

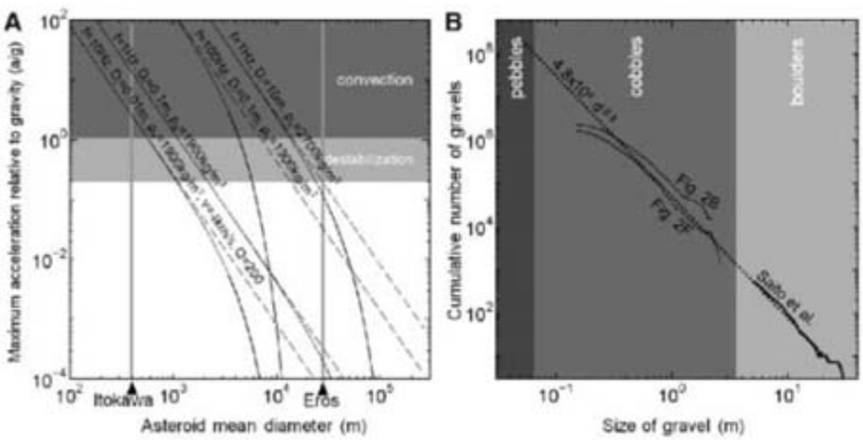

Fig. 4. (**A**) Maximum acceleration of the globally averaged vibration caused by an impact relative to the surface gravity (*a*/*g*) as a function of the size of a stony asteroid. Terrestrial experiments indicate that the gravel destabilization occurred at *a*/*g* ~ 0.2 (*20*) and the granular convection at *a*/*g* slightly larger than unity (*15*). Seismic efficiency, velocity of impact, impactor density, seismic diffusivity, and seismic quality factor are, respectively, 10^{-4}, 5 km^{-1}, 2500 kgm^{-3}, 0.25 km^2s^{-1}, and 2000, except as otherwise noted. These parameter values are given to show the general trend that, for a smaller asteroid, it is easier to achieve a higher *a*/*g* (*27*). (**B**) Preliminary cumulative size distributions (maximum horizontal dimensions) of gravels based on 1150 cobbles in images of Fig. 2, B and F, superimposed on the same plot for 534 boulders in global images (*6*). The distributions generally show a log-log slope of about −2.8 (dotted line), which gives an estimate of the amount of pebbles as 1.9×10^5 m^3 (*27*).

interior, where they can clog the gaps between larger blocks, providing sufficient communication between larger blocks to retain seismic energy while allowing the internal voids to survive.

Particle segregation resulting from migration/vibration is not uncommon in terrestrial laboratory experiments (*17*). Moreover, vibrational size sorting is likely to be more efficient on a smaller body as the threshold velocity for size segregation is theoretically proportional to $\sqrt{g}$ (*25*), where g is the gravity plus rotational acceleration (ranging from 6 to 9 micro-g on Itokawa). Thus, granular convection might not have been limited to the smooth terrains but might have occurred globally. In this case, larger gravels are stranded at the surface to form rough terrains, whereas finer particles migrate beneath and are exposed at potential low areas. Segregation can also be due to other factors. For example, smaller gravels usually have higher mobility because of their lower friction angle (*20*), a smaller mean free path needed for particle migration (*26*), or a smaller amplitude of vibration needed for mobilization, leading to a longer period of migration (*23*). In all cases, variations in particle mobility can explain how gravity-induced global gravel migrations have resulted in the segregation of fines and the formation of smooth terrains, and why boundaries between smooth and rough terrains appear relatively sharp (Fig. 1A).

Our view of Itokawa as a granular mechanical construct is further supported by the total volume of pebbles (2.3×10^5 m^3) (fig. S1) estimated from the total area of smooth terrains (0.075 km^2) (fig. S1). This volume cannot be explained by ejecta from the largest craters on Itokawa but is consistent with those estimated from the cumulative number of boulders (Fig. 4B) (*27*). Thus, pebbles in smooth terrains likely share their origin with boulders in rough terrains. Some cobbles in the close-up images have bright dots on their surfaces (Fig. 2), which are plausibly the remnants of micrometeoroid impact. If so, their number density likely represents the period of time that the cobble is exposed to the space. The number density for a cobble is independent of the roundness or smoothness of the cobble, which varies in each image. This likely indicates that the degradation of cobbles has occurred regardless of their durations of being located at the surface, implying that the cobbles have degraded due not to micrometeoroid impacts but to grindings against other gravels as a result of their collisional histories in orbit or the granular processes discussed above.

References and Notes

1. Regolith is loosely defined as any particulate covering an asteroid. We use the terminology of sedimentary deposits (pebble, cobble, and boulder represent objects whose sizes range from 4 mm to 6.4 cm, 6.4 cm to 2.6 m, and >2.6 m, respectively, with "gravel" including all of them) (*6*).
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Molecular Basis of the Shish-Kebab Morphology in Polymer Crystallization

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In the rich and long-standing literature on the flow-induced formation of oriented precursors to polymer crystallization, it is often asserted that the longest, most extended chains are the dominant molecular species in the "shish" of the "shish-kebab" formation. We performed a critical examination of this widely held view, using deuterium labeling to distinguish different chain lengths within an overall distribution. Small-angle neutron-scattering patterns of the differently labeled materials showed that long chains are not overrepresented in the shish relative to their concentration in the material as a whole. We observed that the longest chains play a catalytic role, recruiting other chains adjacent to them into formation of the shish.

With their low cost and wide diversity in polymer chain structures, polyolefins are the most widely used family of synthetic polymers today. As with many polymers, in their solid form they are neither fully crystalline nor amorphous; instead they are considered semicrystalline with a crystal fraction strongly dependent on processing conditions. The morphologies of semicrystalline materials strongly affect their physical properties (*1*), and control of the structural hierarchy from subnanometer- to micrometer-length scales is thus important technologically and fascinating scientifically. The most notable changes in structure and properties are associated with the flow-induced transition from a relatively isotropic, spherulitic morphology to a highly oriented, shish-kebab morphology, which markedly increases stiffness (*2*) and decreases permeability (*1*). This morphological transition is induced by flow and is very sensitive to the molecular attributes of the polymer—particularly those of the longest chains present in the material. Recent advances in catalyst technology afford control of not only the monomer-level structure of the polymer chain (*3*, *4*) but also the topology (*5*) and the nanostructure (*6*) of olefinic polymers. Therefore, there is an increasing impetus to uncover the ways in which these molecular attributes affect flow-induced crystallization.

It is well known that a beautiful superstructure of polymer crystals can be created by crystallization during flow (*7*). This super-

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structure is composed of threadlike cores that are encircled with platelike lamellar crystals. Although this shish-kebab morphology was first observed in the mid-1960s (*8*–*10*), the mechanism of shish-kebab formation is still a topic of ongoing debate (*11*–*18*).

Over the past few decades, many investigators have adopted the ideas of Keller and co-workers, who proposed that the threadlike shish form when some of the chains undergo a transition from a coiled conformation to a highly elongated state during flow (*19*–*21*). According to the coil-stretch theory, the longest chains are mainly responsible for shish-kebab formation, considering that for specified flow conditions, only chains longer than a threshold chain length M^* undergo the coil-stretch transition. Recent simulations of flow-induced crystallization from a solution of short and long chains have shown that "long chains stretched and subsequently formed a shish core around which the short chains aggregate in a kebab" (*14*). Similarly, simulations of flow-induced crystallization from a melt of short and long chains concluded that "crystallization of oriented long chains" forms the shish and the short chains crystallize "from the lateral side of long-chain crystals" (*17*). Hsiao and co-workers have even proposed that long chains are quantitatively separated into shish, such that the fraction of chains longer than M^* can be equated with the shish content (*22*).

Using small-angle neutron scattering (SANS) with deuterium labeling of specific chain lengths in an overall distribution, we examined polymer crystallization for flow-extended chains. Three model isotactic polypropylene (iPP) resins with well-matched overall molar mass distributions—but different chain lengths labeled with deuterium—were prepared by blending hydrogenated and deuterated polymers that were produced using a metallocene catalyst (*23*). Similar to the work of Waymouth and co-workers (*24*), these three model resins contained labeled chains in the shortest third, the middle third, or the longest third of the overall distribution, denoted Short D, Medium D, and Long D, respectively (Table 1). We chose iPP for this study because we know the threshold stress required to induce shish in a material of this molar mass distribution (*25*, *26*); we also know that chains 4.5 times longer than those with the number-average molecular weight (M_n) are effective in promoting shish formation (*11*), whereas chains less than or equal to twice the mean have no discernable effect. We have extensive experience with inducing shish at a temperature where negligible growth occurs and then revealing them by cooling to a temperature where growth proceeds out into the relaxed melt.

Each of the deuterium-labeled resins was subjected to identical flow and thermal history to form specimens that had a skin-core morphology (*25*). The labeled polymers were sheared for 1.0 s under isothermal conditions at 180°C by pressure-driven flow through a thin rectangular channel with a wall shear stress of 0.14 MPa. Immediately after cessation of flow, the flow cell was cooled to 140°C over 10 min and then held at 140°C for 20 min. The transient response during and after flow, as well as final morphology, was consistent for the three samples. During the shear pulse, all three materials showed similar birefringence traces, characteristic of formation of oriented precursors (*11*). During cooling, the onset of crystallization for all three materials was observed when the temperature reached approximately 160°C. The marked rise in birefringence during crystallization was almost identical for the three samples. The transmittance signature of impingement of the oriented skin was observed for all three samples approximately 5 min after the temperature reached 140°C, and the transmittance fell to approximately 5% by the end of the 20-min holding time (figs. S1 and S2). The flow cell was then quenched in cold water to complete solidification and the sample was removed for ex situ characterization by optical and electron microscopy, wide-angle x-ray scattering (WAXS), small-angle x-ray scattering (SAXS), and SANS.

Microscopy, WAXS, and SAXS confirmed that on scales from subnanometer to micrometer, the three materials had the same semicrystalline morphology (figs. S3 to S7). In particular, all three samples had an oriented skin with a thickness of approximately 70 μm near each wall (fig. S3), where the shear stress ranged from 0.10 to 0.14 MPa. The shish-kebab nanostructure observed in the oriented skin by transmission electron microscopy was indistinguishable for the three materials (fig. S4).

The highly oriented morphology (Fig. 1A) consisted of stacks of parent lamellae orthogonal to the flow direction and, characteristic of iPP, epitaxial daughter crystallites (oriented approximately ±80° with respect to the parent lamellae). Coherent orientation of the parent lamellae results from nucleation on threadlike precursors. Crystallites were approximately 15 nm thick, arranged in periodic stacks with a period of about 30 nm, or long spacing. Shish appeared to be approximately 300 nm apart. The x-ray scattering pattern of this oriented morphology (Fig. 1B) had strong lobes of scattered intensity from the stacks of parent lamellae (meridional) and weaker scattering from the daughter lamellae (equatorial), consistent with the small, poorly defined stacks of daughter lamellae seen in the micrograph. Scattering angles consistent with the separation between shish were obscured by the beamstop.

In the final solid state, very different SANS patterns were observed as a function of the length of the labeled chains (Fig. 2A, far left column). Parent lamellar stacks were clearly evident in all three samples as the lobes of intensity in the meridional direction; strong equatorial scattering was evident near the beamstop. The sample containing deuterated short chains exhibited much stronger scattering than those with labeled medium or long chains. This is consistent with the ease with which short chains can be "reeled in" to the growth face of a crystallite (*27*). In Short D, the deuterium label became concentrated in the lamellar crystallites. Because their coil dimensions are smaller than the long spacing, the short

Table 1. Weight-average molecular weight mass (M_w) and polydispersity (M_w/M_n) of the deuterium-labeled fraction and of the blend as a whole. Each blend contains 13 weight % labeled chains. Composition and preparation of blends are described in supporting online material text and tables S1 and S2.

	Deuterium-labeled species		Blend	
	M_w (kg/mol)	M_w/M_n	M_w (kg/mol)	M_w/M_n
Short D	41	2.4	467	8.3
Medium D	197	3.2	486	7.9
Long D	1781	3.1	557	8.6

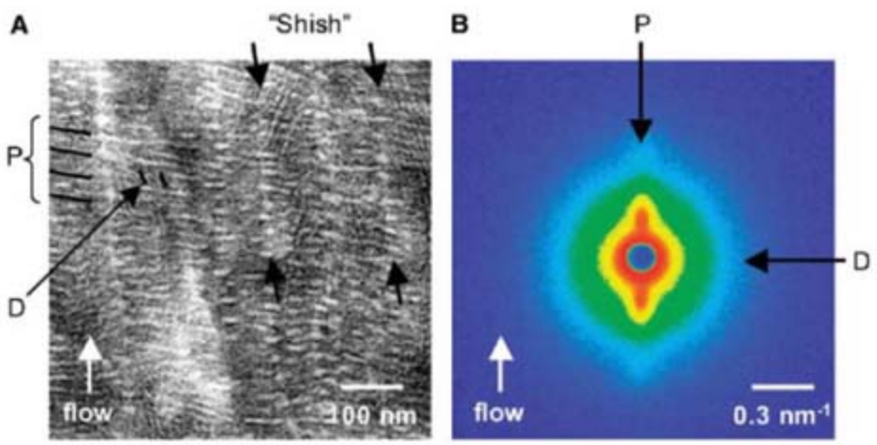

Fig. 1. (**A**) Transmission electron micrograph of a stained section of the oriented skin showing shish oriented along the flow direction, parent lamellae (P), and their epitaxial daughters (D). (**B**) Small-angle x-ray scattering pattern taken with beam along the velocity gradient direction showing that stacks of parent lamellae orthogonal to the flow contribute to the vertical lobes (P) and that daughter lamellae contribute to equatorial intensity (D). All three differently labeled blends display the same solid-state morphology (figs. S3 to S7). The data shown are for the Short D specimen.

chains rarely form tie chains between neighboring lamellae, so few of their segments become trapped in the interlamellar region. Thus, the short chains abandon the interlamellar region, but medium and long chains are trapped there, both because they cannot add to the growth front as quickly as it passes by and because they are more likely to be frustrated by attaching to multiple stacked lamellae. Therefore, the scattering from the lamellar stacks in Medium D and Long D is much weaker and arises from a relative excess of deuterium in the noncrystalline interlamellar material.

At much smaller angles, there is very intense scattering in the equatorial direction that is absent in the meridional direction. The intense scattering orthogonal to the flow direction at small q indicates the existence of long slender objects parallel to the flow direction with lateral separation much greater than the lamellar long spacing. To establish the nature of these long, slender objects, we recorded the SANS pattern at progressively higher temperatures until only melt scattering was observed. The patterns recorded at 180°C were dominated by the melt: Neither crystallites nor anisotropy could be detected (Fig. 2, far right column). The scattering patterns agreed with Gaussian chains in the melt (*28*). At temperatures near the nominal melting temperature, such that most of the crystallites present in the fully solidified state were no longer present, a strongly oriented structure remained (Fig. 2A, middle columns). Parent lamellar stacks were weakly evident at 166°C, consistent with the real-time birefringence indicating that the earliest overgrowth of kebabs formed at approximately 160°C during cooling. The dominant signal was in the small-angle peaks that result from narrow shish-kebabs, which were evident in the SANS patterns of materials labeled on the short or medium chains but not in the long-chain labeled material. At 168°C, the scattering from parent lamellae (kebabs) could not be distinguished from the background, yet the small-angle equatorial signal was still readily observable for Short D and Medium D.

To check for the possibility that weak peaks might be present in the long-chain labeled case but obscured by the relatively strong melt scattering of the long chains, we examined the difference in scattered intensity between 166° and 180°C and between 168° and 180°C. Already at 166°C, very few crystallites were present, so the melt contribution dominated the overall scattering intensity for both Medium D and Long D (which had R_g of ~18 and ~45 nm, respectively). The scattering pattern obtained at 180°C provided a very good approximation of the melt contribution at 166° and 168°C, precisely because the degree of crystallinity was very low, so that $I(q)_{180°C}$ could simply be subtracted from $I(q)_{166°C}$ or $I(q)_{168°C}$ to isolate the crystallite contribution in these scattering patterns. Even after providing a null background on which a weak signal would be evident, there was no sign of small-angle equatorial scattering in Long D (Fig. 3). Therefore, to good approximation, the concentration of deuterated long-chain segments in the shish matched that in the material as a whole. The view that shish are dominated by long chains is not consistent with the observed SANS patterns.

The evidence that the long chain concentration in the shish matches that in the surrounding melt indicates that, as a shish propagates, it incorporates all of the species in its path. For example, if the long chains are representative of the longest 30% of all chains, the lack of neutron contrast in the Long D sample would imply that approximately 70% of the shish constituents are short and medium length chains (to within the ratio of the densities of the melt and shish materials).

The anisotropy of shish scattering in SANS patterns at 168°C of the short- and medium-chain labeled materials is quite distinct, despite its absence for long-chain labeled material. The data are compatible with various scenarios: molecular deformation of short and medium chains in the shish being greater than that of long chains, enhanced fluctuations in the local molar mass distribution due to shear, or a difference in concentration of short and medium chains in the shish relative to the bulk. We conclude that the most likely of these is the last.

It has been established that the presence of long chains greatly enhances the propagation of shish. We offer a physical mechanism that simultaneously explains the importance of long chains for shish formation and the evidence that they are not the dominant species in the shish. We hypothesize that shish propagate by a local mechanism that is active at their ends (and, perhaps, along their sides, adding to their thickness) (*11*). Chains in the immediate vicinity may attach to the surface of the shish, making those chains more susceptible to flow-induced orientation. The degree of orientation that is actually induced in these tethered chains is very sensitive to their length. Given the highly nonlinear dependence of flow-induced crystallization on the macroscopic stress, the probability that melt transforms to crystal must be a strong function of the local segmental orientation of the chains. Therefore, the presence of long chains in the melt could markedly accelerate shish propagation by accessing high degrees of segmental orientation after they adsorb to the tip of a shish (*11*).

If the "coil-stretch transition" of long chains is essential, as proposed by Keller's hypothesis, then it appears that the stretching occurs in long chains that are near the tip of a propagating shish, not throughout the volume as Keller implied. From the morphology that develops, the degree of orientation that the long chains attain elsewhere is rarely sufficient to trigger local ordering. The adsorption of long chains (along with all others) onto the shish surface,

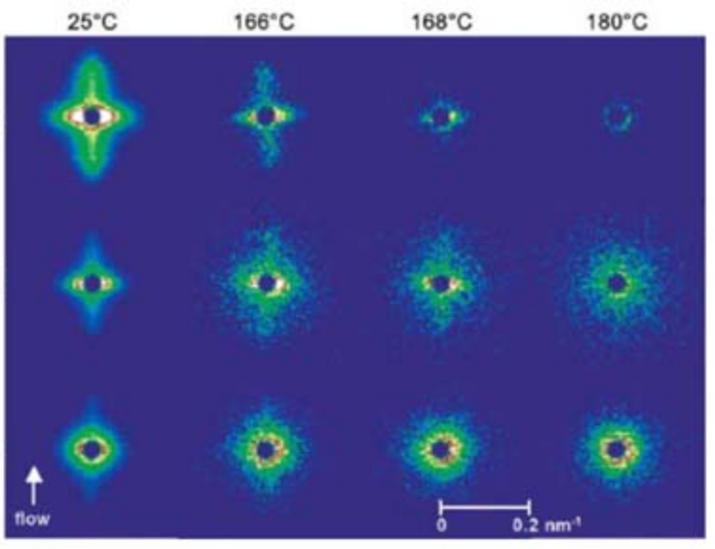

Fig. 2. Temperature dependence of SANS profiles of deuterium-labeled materials during heating from 25° to 180°C. The labeled fraction is denoted by S, M, and L for Short D, Medium D, and Long D, respectively.

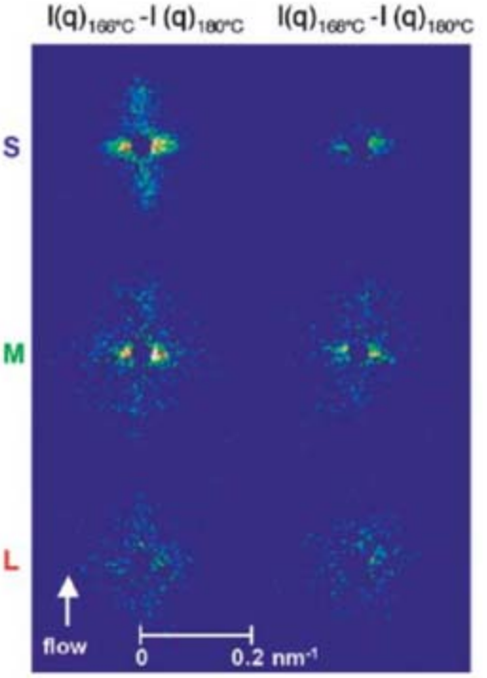

Fig. 3. The change in SANS scattering intensity between 166° and 180°C (**left**) and between 168° and 180°C (**right**) for each of the three deuterium-labeled blends.

combined with the action of flow (which orients the tethered long chains much more than the rest) can explain why long chains enhance shish propagation (*11*). The elevated orientation created near the shish causes rapid ordering.

It has been shown that during flow, shish can increase in length by micrometers per second (*26*). The time it takes for a shish to overtake a typical long- or medium-length chain ($\Delta t \approx$ 1 ms) is too fast for its center of mass to diffuse out of or into the path of propagation. In $\Delta t =$ 1 ms, even a medium-length chain of 200 kg/mol chain diffuses less than 1 nm; i.e., $(D\,\Delta t)^{1/2} <$ 1 nm (*29*). There simply is not enough time to segregate the long chains from the bulk into the shish. Thus, long chains greatly enhance the propagation velocity of shish, with the kinetic consequence that all lengths of chains become incorporated as the shish advances.

Direct measurement of chains of different lengths partitioning into the shish shows that the fraction of long-chain segments within the shish matches their composition in the melt as a whole. This finding is consistent with previous literature showing that the longest chains play a central role in the formation of shish. The two observations taken together indicate that the long chains recruit neighboring chains to join them in forming the shish. The physical picture is consistent with the observations of Rutledge and co-workers in their simulations of nucleation from the melt: Molecular mobility and relaxation of a number of neighboring segments into crystalline-like order is vital to the formation of nuclei from an oriented melt (*30*).

The implications of molecular-level understanding of the formation of the highly oriented morphology in semicrystalline polymers are widespread. Judicious choice of the concentration and length of long chains can be used to tune the properties of the oriented skin that are vital to applications ranging from biomedicine to transportation: Surface hardness, impact resistance, reflectivity, and adhesion, among many other qualities, depend upon the microstructure near the surface. The realization that shish formation involves all chain lengths underscores the potential for further expansion of the diversity of material properties that can be achieved using the same basic set of monomers.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 to S7
Tables S1 and S2
References

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Mesoscale Eddies Drive Increased Silica Export in the Subtropical Pacific Ocean

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Mesoscale eddies may play a critical role in ocean biogeochemistry by increasing nutrient supply, primary production, and efficiency of the biological pump, that is, the ratio of carbon export to primary production in otherwise nutrient-deficient waters. We examined a diatom bloom within a cold-core cyclonic eddy off Hawai'i. Eddy primary production, community biomass, and size composition were markedly enhanced but had little effect on the carbon export ratio. Instead, the system functioned as a selective silica pump. Strong trophic coupling and inefficient organic export may be general characteristics of community perturbation responses in the warm waters of the Pacific Ocean.

Mesoscale eddies in the world's oceans are ubiquitous and bring episodic pulses of new nutrients into the photic zone. Their ephemeral nature, however, makes them difficult to study (*1*), and their biogeochemical importance remains controversial (*2*, *3*). The E-Flux project was designed to exploit the reliable presence of one type of commonly occurring wind-driven mesoscale eddy that forms in the lee of the Hawaiian Islands (*4*, *5*). This region thus serves as a natural laboratory for investigating eddy-enhanced production and particle export in an oligotrophic subtropical ecosystem (*1*, *6*–*8*). Here, we report the physical and biogeochemical dynamics of a first baroclinic mode eddy, Cyclone Opal, which became visible in Moderate Resolution Imaging Spectroradiometer (MODIS) and Geostationary Operational Environmental Satellite (GOES) imagery between 18 and 25 February 2005.

Cyclone Opal appears to have originated between the islands of Maui and Hawai'i because of strong and persistent northeasterly trade winds. Under these conditions, the wind stress curl drives Ekman pumping, leading to doming of isopycnal surfaces (*4*, *5*). Shipboard measurements (10 to 22 March) confirmed that Cyclone Opal was a well-developed cold-core eddy as evidenced by its size, tangential current speeds, vertical isopycnal displacements, and outcroppings of density and nutrient surfaces (Figs. 1 and 2). Within this feature, a core region of high biomass that supported euphotic zone primary production (PP) (*9*) rates two- to threefold higher than surrounding oligotrophic waters (Table 1) was confined to an area less than 40 km in diameter. A strongly developed diatom bloom occurred in the deep chlorophyll maximum (DCM) of the eddy's core isopycnal surfaces (σ_t = 24.2 to 24.4 kg m^{-3}) that had been uplifted to 60- to 80-m depth. Cyclone Opal was tracked by a shipboard acoustic Doppler current profiler as it moved ~165 km

southward with an average translational speed of 8 km day^{-1}. Although the eddy maintained its primary physical features and mesoscale structure throughout these observations, the biogeochemistry of the core region evolved substantially. Cyclone Opal therefore provided an intriguing glimpse into a nutrient-perturbed oceanic community entering its biologically declining phase.

The biological community within Cyclone Opal was vertically heterogeneous, with a strong subsurface diatom bloom superimposed onto a typical oligotrophic community of smaller photoautrophic cells (Fig. 2 and Table 1). Initially, large (>20 μm) diatoms in the DCM were enhanced by almost 100-fold above background levels, with a 60-fold increase in the biomarker fucoxanthin (Fig. 3). Diatoms also composed 78% of the highest biomass observed in Cyclone Opal (89 μg C l^{-1}, Fig. 3), with about half attributed to two centric genera, *Rhizosolenia* and *Chaetoceros*. In contrast, DCM communities outside the eddy were dominated by small autotrophs (80% of biomass had cells <10-μm), such as prymnesiophytes, pelagophytes, and *Prochlorococcus* spp. In general appearance as well as total biomass and size composition, Cyclone Opal's bloom bore a striking similarity to the iron-induced bloom observed during the Southern Ocean Iron Experiment (*10*). Cyclone Opal was notably not dominated by pennate diatoms, as occurred in iron-fertilized equatorial waters (*11*).

Contributing to the vertical heterogeneity within Cyclone Opal was a distinct and persistent layer of decaying and senescent diatom cells directly above the DCM. Epifluorescence microscopy indicated that ~90% of these cells were lacking in chlorophyll and/or cellular protein, and fast repetition rate fluorometry (FRRF) indicated that photochemical energy conversion efficiency was depressed [variable fluorescence/maximal fluorescence (F_v/F_m) = 0.34 at 50 to 60 m versus 0.49 at 70 to 80 m]. These differences in diatom physiological state suggest that the bloom began as nutrients were uplifted into lit surface waters and then declined because of nutrient limitation. This decline enabled light penetration and diatom growth to extend to deeper waters.

Cyclone Opal's biological evolution was readily apparent from 16 to 21 March. Daily observations within the DCM showed an 80% decrease in diatom biomass and a 70% decrease in fucoxanthin (Fig. 3). During this period, the diatom assemblage transitioned to lightly silicified genera *Hemiaulus* and *Mastogloia* and smaller pennate forms more common in surrounding waters (*12*). These community changes were accompanied by a gradual DCM decline in F_v/F_m (from 0.51 to 0.41), and the light-limited rate of photosynthesis decreased from 0.07 to 0.04 [mg C mg chlorophyll a (chl a)$^{-1}$ hour^{-1}] (mmol quanta m^{-2} s^{-1})$^{-1}$. These results are consistent with a transition in plankton community metabolism from net autotrophy to heterotrophy (*9*).

We investigated plankton growth and grazing during this decline (*9*). Diatom growth rate was indistinguishable between eddy core and surrounding waters when integrated over the entire euphotic zone. However, there was substantial depth variability within Cyclone Opal, with highest diatom growth at the DCM [0.57 ± 0.18 day^{-1} (mean ± SD) at 70 to 80 m; n = 6 measurements] and the lowest diatom growth directly above at 50 to 60 m (0.23 ± 0.25 day^{-1} at 50 to 60 m; n = 9), corresponding to healthy and senescent diatom layers, respectively. Substantial net diatom growth only occurred in the DCM (0.26 ± 0.12 day^{-1}; n = 6) yet was accom-

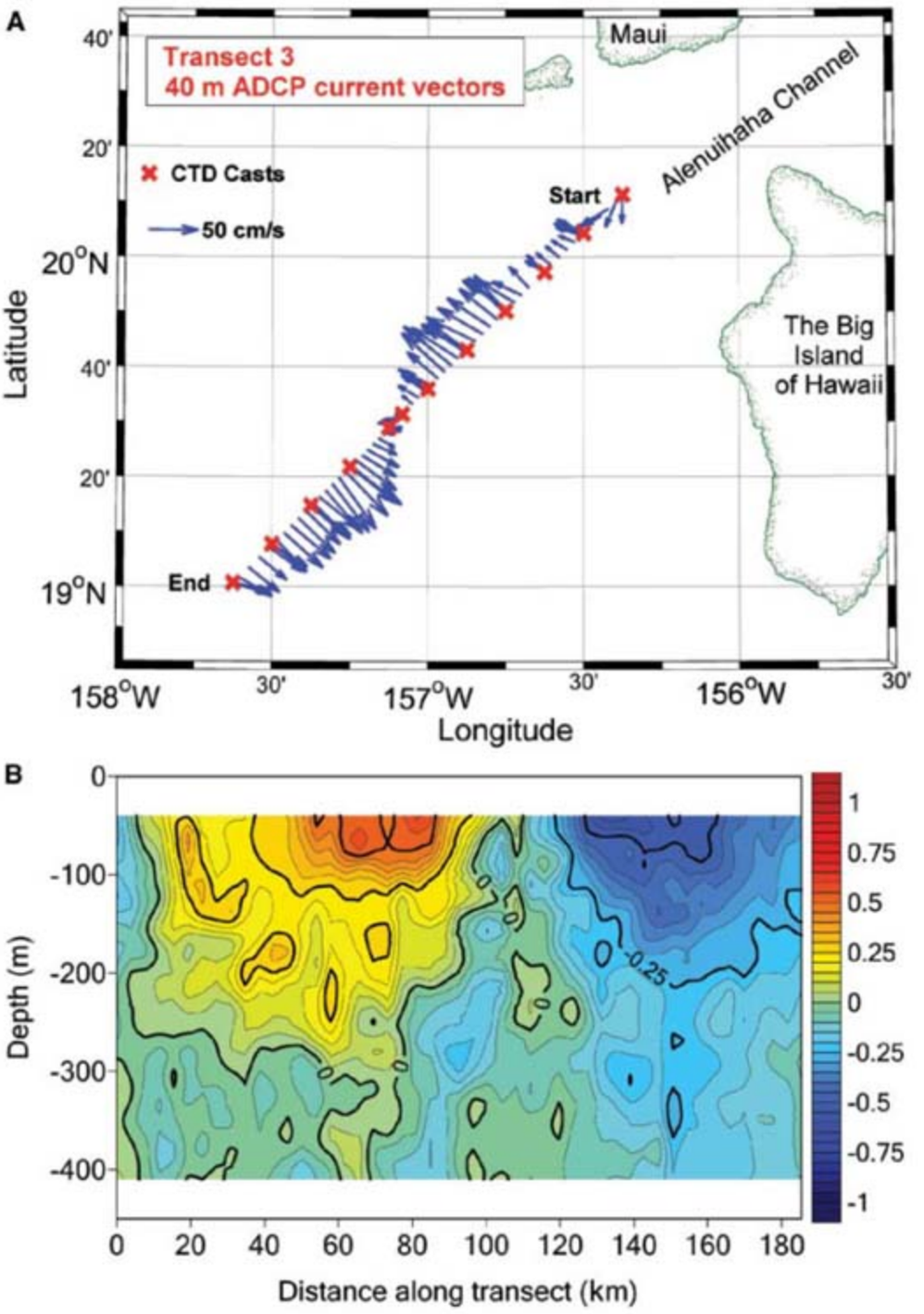

Fig. 1. Spatial distribution of the areal extent of Cyclone Opal during transect 3 as depicted by (**A**) 40-m current vectors and (**B**) sectional perpendicular velocities (m s^{-1}).

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panied by higher diatom mortality by microherbivore grazing (0.31 ± 0.26 day^{-1} versus 0.21 ± 0.14 day^{-1}). In contrast, within the senescent diatom zone, grazing losses yielded negligible net diatom growth (0.02 ± 0.20 day^{-1}; $n = 9$).

On the basis of these experiments, it appears that reduced growth rate rather than a grazing surge precipitated diatom demise, which is consistent with observed distributions of senescent and healthy cells. Although the ultimate cause of diatom decline remains elusive, it may be due to silicic acid limitation. The ratio of silica (Si) to nitrogen (nitrate plus nitrite, N+N) availability was strongly depressed in the eddy core (Table 1). In the senescent zone, silicic acid concentrations were below detection (<0.35 μM) during initial sampling. Furthermore, in a series of experiments under simulated in situ conditions, phytoplankton from the eddy core DCM did not respond to varying combinations of added nitrate, phosphate (P), and iron (*9*). In contrast, experiments in surrounding waters showed a strong and rapid recovery response of F_v/F_m in all nitrate addition treatments, implying nitrate limitation. Taken in combination, low concentrations of silicic acid and the lack of phytoplankton community response to additions of nitrate, P, and iron strongly suggest that DCM populations were Si-limited.

We then considered a hypothetical upper limit to organic carbon export efficiency where all new nutrients (N+N) lifted into the sunlit layer are eventually returned to depth as organic particles with an assumed canonical Redfield C/N ratio of 6.6. The contribution of new production that could be attributed to bloom decline was determined through a salt budget based on uplifted isopycnal density surfaces within the eddy core (*9*). About 147 ± 32 mmol m^{-2} of N+N was initially brought into the euphotic zone (Table 1). If all uplifted N+N were used by phytoplankton, the potential new production during the roughly 4- to 5-week lifetime of Cyclone Opal is equivalent to half of the annual new production in this region [2.0 mol C m^{-2} year^{-1} above 100 m (*13*)] and is almost 10 times higher than the amount directly observed (Table 1). We hypothesize that Si limitation of diatoms coupled with enhanced grazing results in efficient C remineralization but enhanced biogenic silica export, consistent with the model proposed by Dugdale *et al.* (*14*) for high-nutrient low-chlorophyll waters.

Microzooplankton consumers accounted for most of the utilization of diatom production, as evidenced by a lack of fecal pellets and denuded diatom frustules. As a consequence, the fate of diatom production was toward remineralized C, N, and P and empty diatom frustules within the euphotic zone, rather than the rapid export of organic-rich large particles, e.g., compacted fecal pellets or aggregates of intact diatoms. Strong microzooplankton grazing relative to macrozooplankton grazing facilitated recycling and greatly diminished the potential for high export ratios of C and associated bio-elements from the wind-driven eddy-stimulated bloom (Table 1).

This hypothesis is further supported by bacterial community composition, total organic carbon (TOC) accumulation, and particulate C (PC) and N (PN) export rates. Mixed layer bacterioplankton communities were similar to those measured outside the eddy. Below 50 m, however, *Planctomycetes*, *Bacteroidetes*, and certain *Proteobacteria* thought to degrade high–molecular weight dissolved organic matter appeared (*15*–*17*). TOC concentrations within the upper 110 m increased by 600 mmol C m^{-2} (expected versus observed, Table 1). In contrast, PC and PN exports were only minimally enhanced within the eddy core (Table 1) and were similar to those in nearby oligotrophic waters at station (Sta.) ALOHA (Hawai'i Ocean time series program) (*13*, *18*).

Collectively, our results suggest that Cyclone Opal was surprisingly inefficient in transporting PC

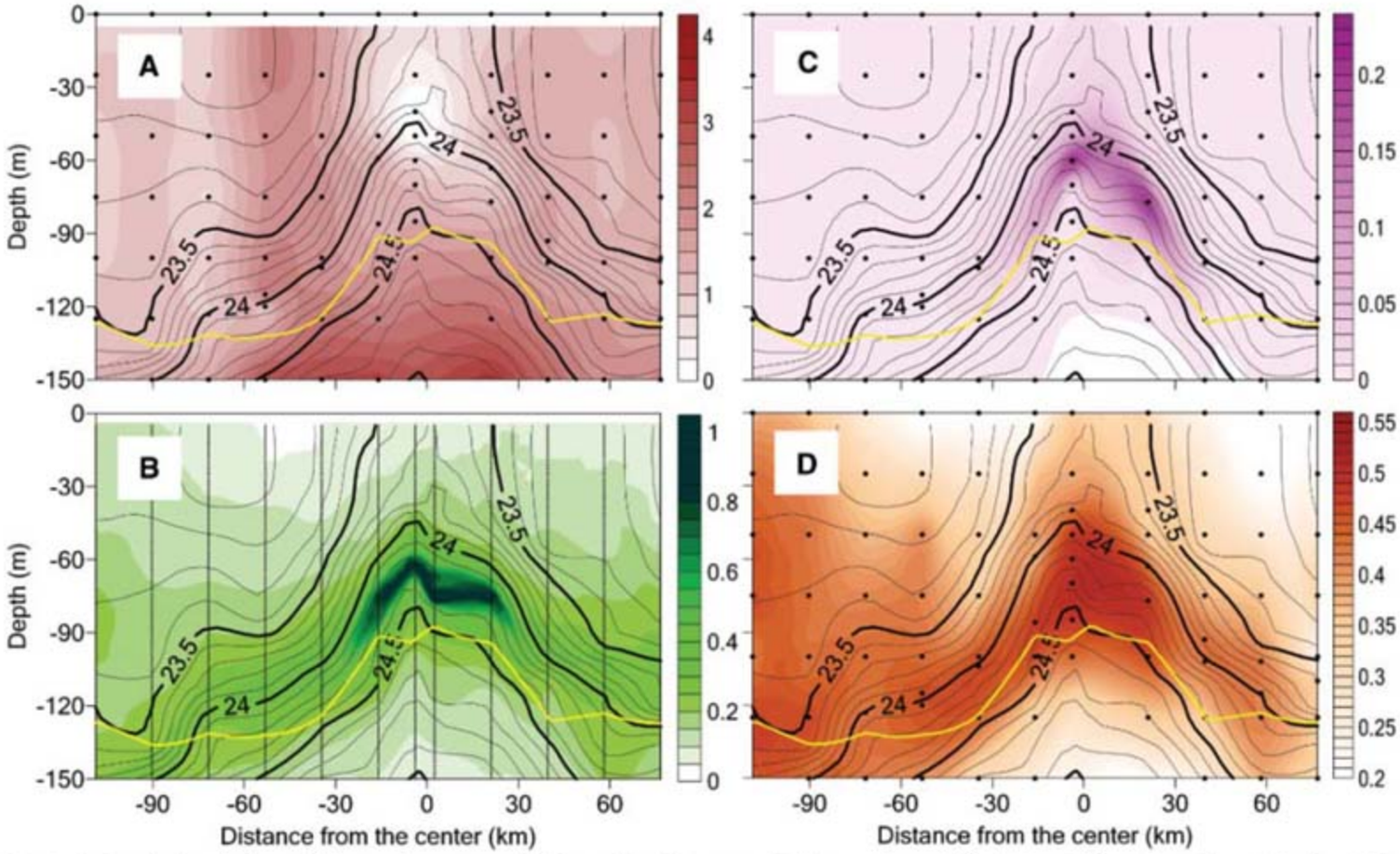


Fig. 2. Sectional views (horizontal distance from center of eddy and depth) for transect 3. Contour lines indicate the depth of isopycnal surfaces: (**A**) silicic acid (μM), (**B**) total chlorophyll a (TChl a, mg m^{-3}), (**C**) fucoxanthin (mg m^{-3}), and (**D**) photochemical energy conversion efficiency (F_v/F_m). TChl a is derived with the relationship between conductivity temperature depth (CTD) fluorometer voltage (Flu) and high-performance liquid chromatography (HPLC)–measured TChl a by using a third-order regression curve (TChl a = $0.31 \times \text{Flu}^3 - 0.80 \times \text{Flu}^2 + 1.09 \times \text{Flu} - 0.02$; $r^2 = 0.85$). The yellow line in each contour represents the 1% light level. The 1% light level depth was computed by using the following relationship: $\log_{10}Z_e = -0.64429(\log_{10}C) + 1.16115$, where Z_e is the 1% light level depth and C is the mean value of the chlorophyll concentration between 0 and Z_e. $\log_{10}Z_e$ and $\log_{10}C$ were first computed for casts collected during daylight hours and interpolated (*29*).

to depth. Although gross PP (GPP) rates were elevated by over a factor of 2, the ratio of PC export to GPP remained low at 0.05, similar to that measured at Sta. ALOHA (*19*) and other open-ocean ecosystems (*20*). More than 85% of net community production (NCP) accumulated as TOC in the water column (Table 1) (*9*). Although this finding is consistent with the pelagic food web model of Laws *et al.* (*21*), which predicts that export ratios do not vary with total production at temperatures greater than ~25°C, the export ratio is substantially less than commonly associated with large-scale diatom blooms (*22*).

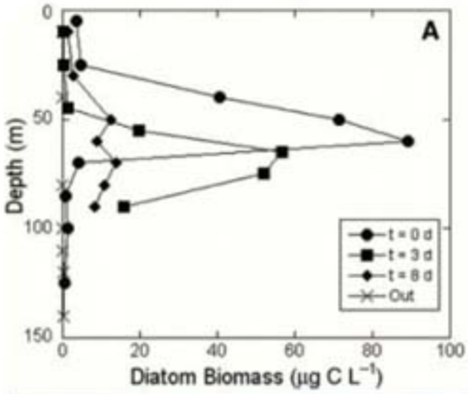
Table 1. Water column properties of IN versus OUT stations occupied during the E-Flux III cruise (values in parentheses correspond to the number of observations). Mixed layer depth is defined as the depth at which seawater temperature is 1°C less than the temperature at 10 m. All observed (^{obs}) nutrient data were averaged over the upper 110 m in all control (OUT, $n = 3$) and IN stations ($n = 7$), which include the center station from transect 3 depicted in Fig. 1. Expected nutrient data (^{exp}) for IN stations was determined by using a salt budget based on the isopycnal uplift and compaction of density surfaces (*9*). GPP and NCP calculated from $\Delta^{17}O$ were determined over the depth of the mixed layer. GPP and NCP from $\Delta^{17}O$ were not determined at the OUT station during the March 2005 cruise. As such, average values were used from two previous cruises in November 2004 and January 2005 from the same OUT station location. All biological and pigment data, as well as PP derived from phytoplankton growth, were averaged to depths just below the 1% light level within the eddy core (0 to 110 m, center station from transect 3 and the first three eddy core stations, for example, before bloom decline, $n = 4$) and 0 to 150 m at control stations ($n = 3$). Taxon-specific pigments include fucoxanthin (diatoms), chlorophyllide a (degradation pigment associated with senescent and grazed diatoms), divinyl chlorophyll a (*Prochlorococcus* spp.), and zeaxanthin (all cyanobacteria).

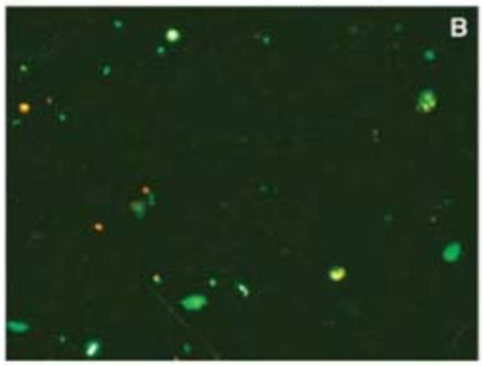
	Inside Opal	Outside Opal	IN/OUT or Δ
Mixed layer depth (m)	51 ± 8 m ($n = 48$)	95 ± 7 m ($n = 48$)	-
1% light level (m)	89 ± 10 m ($n = 20$)	132 ± 19 m ($n = 18$)	-
N+ N (0 to 110 m, mmol N m^{-2})	91 ± 15 ($n = 7$)^{obs}	24 ± 5 ($n = 3$)	3.8^{obs}
	147 ± 32 ($n = 3$)^{exp}		6.1^{exp}
Phosphate (0 to 110 m, mmol P m^{-2})	17.1 ± 2.5 ($n = 7$)^{obs}	9.8 ± 1.8 ($n = 3$)	1.7^{obs}
	25.9 ± 4.6 ($n = 3$)^{exp}		2.6^{exp}
Silicic acid (0 to 110 m, mmol Si m^{-2})	166 ± 30 ($n = 7$)^{obs}	170 ± 41 ($n = 3$)	1.0^{obs}
	244 ± 50 ($n = 3$)^{exp}		1.4^{exp}
TOC (0 to 110 m, mol C m^{-2})	7.26 ± 0.22 ($n = 6$)^{obs}	7.91 ± 0.03 ($n = 3$)	0.9^{obs}
	6.66 ± 0.26 ($n = 3$)^{exp}		0.8^{exp}
Si/N ratio	1.8 ± 0.5 ($n = 7$)^{obs}	7.1 ± 2.2 ($n = 3$)	
N/P ratio	5.3 ± 1.2 ($n = 7$)^{obs}	2.4 ± 0.7 (n = 3)	
PP from phytoplankton growth (mmol C m^{-2} day^{-1})	128 ± 16 ($n = 3$)	46 ± 13 ($n = 3$)	2.8
GPP from $\Delta^{17}O$ (mmol C m^{-2} day^{-1})	125 ± 6 ($n = 2$)	51 ± 27 ($n = 3$)	2.5
TChl a (mg m^{-2})	32.1 ± 4.9 ($n = 4$)	29.1 ± 1.8 ($n = 3$)	1.1
Fucoxanthin (mg m^{-2})	5.5 ± 1.6 ($n = 4$)	1.0 ± 0.02 ($n = 3$)	5.5
Chlorophyllide a (mg m^{-2})	3.2 ± 1.1 ($n = 4$)	0.2 ± 0.2 ($n = 3$)	16
Divinyl chlorophyll a (mg m^{-2})	7.6 ± 1.1 ($n = 4$)	13.7 ± 1.1 ($n = 3$)	0.6
Zeaxanthin (mg m^{-2})	5.3 ± 0.7 ($n = 4$)	9.7 ± 0.3 ($n = 3$)	0.5
Phytoplankton biomass (mmol C m^{-2})	220 ± 35 ($n = 4$)	114 ± 7 ($n = 3$)	1.9
Diatom biomass (mmol C m^{-2})	141 ± 39 ($n = 4$)	3 ± 2 ($n = 3$)	47
Prochlorococcus spp. (mmol C m^{-2})	32 ± 5 (n = 4)	58 ± 16 ($n = 3$)	0.6
Protozoan grazers (mmol C m^{-2})	78 ± 12 ($n = 4$)	59 ± 11 ($n = 3$)	1.3
Heterotrophic bacteria (mmol C m^{-2})	71 ± 7 ($n = 4$)	80 ± 7 ($n = 3$)	0.9
NCP based on dissolved inorganic C, TOC, and N+N mass balance (mmol C m^{-2} day^{-1})	14.0 ± 4.4	2.5 ± 1.9	5.6
NCP from $\Delta^{17}O$ and O_2/Ar (mmol C m^{-2} day^{-1})	6.6 ± 7.5 ($n = 2$)	2.5 ± 1.0 ($n = 3$)	2.6
PC export at 150 m (mmol m^{-2} day^{-1})			
Traps	1.54 ± 0.11 ($n = 3$)	1.52 ± 0.20 ($n = 3$)	1.0
^{15}N mass balance	2.79 ± 0.8	1.39 ± 0.46	2.0
^{234}Th derived	0.97 ± 0.57 ($n = 5$)	0.85 ± 0.08 ($n = 3$)	1.1
PN export at 150 m (mmol m^{-2} day^{-1})			
Traps	0.15 ± 0.01 ($n = 3$)	0.16 ± 0.02 ($n = 3$)	0.9
^{15}N mass balance	0.42 ± 0.13	0.21 ± 0.07	2.0
^{234}Th-derived	0.07 ± 0.04 ($n = 5$)	0.05 ± 0.01 ($n = 3$)	1.4
PSi export at 150 m (mmol m^{-2} day^{-1})			
Traps	0.427 ± 0.034 ($n = 3$)	0.111 ± 0.065 ($n = 3$)	3.8
^{234}Th-derived	0.145 ± 0.110 ($n = 5$)	0.100 ± 0.027 ($n = 2$)	1.5

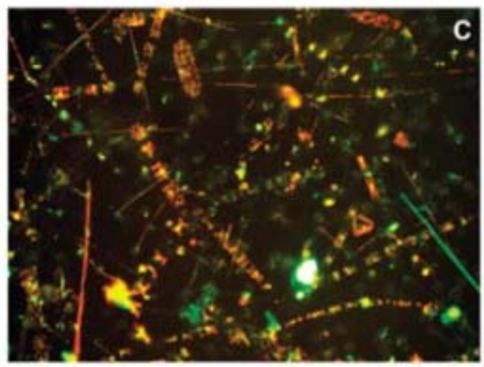
Although PC export only modestly increased in Cyclone Opal, the biogenic particulate silica (PSi) flux was enhanced by 1.5 to 4 times more than fluxes at control stations, Sta. ALOHA (0.085 ± 0.058 mmol Si m^{-2} day^{-1}), and other oligotrophic open-ocean sites (e.g., Sargasso Sea, 0.107 ± 0.036 mmol Si m^{-2} day^{-1}) (*23*) (Table 1). Within the eddy, high PSi fluxes relative to PC fluxes were confirmed by visual observations of empty diatom frustules in sediment trap material and an increase in PSi/PC ratios sampled at 150 m during the time series. For comparison, these eddy-induced PSi fluxes were similar in magnitude to those observed in the more productive equatorial Pacific (~0.330 mmol Si m^{-2} day^{-1} at 200 m) and had PSi/PC molar ratios more than double those found there (*24*) and at Sta. ALOHA.

This study provides a direct biogeochemical quantification of the decline and fate of an eddy-stimulated diatom bloom in the oligotrophic open ocean. Although our results confirm that wind-driven first baroclinic mode cyclonic eddies are highly productive and increase biomass (*1*, *6*, *8*), they are not necessarily more efficient in exporting PC and PN to deep waters. The observation that eddy-enhanced production only yields a proportional increase in C export is at odds with the general perception that marked increases in the export/production ratio follow major shifts in community size structure from small to large phytoplankton (*25*, *26*). Nonetheless, the surprisingly low export efficiency in Cyclone Opal is consistent with models of temperature effects on export production (*21*), as well as warm-water diatom blooms induced by iron fertilization in the equatorial Pacific (*11*, *27*). Here, the unusual occurrence of a centric diatom bloom residing relatively deep in the euphotic zone seems to represent ideal conditions for a major flux event. The absence of disproportionate organic export fluxes under these circumstances argues that strong microbial community coupling of production, grazing, and remineralization processes in warm-water Pacific ecosystems may dampen nutrient-perturbation effects on the C export ratio.

Episodic inputs of nutrients and trace elements into surface waters by eddies, fronts, and human manipulation have been widely invoked as mechanisms that enhance C sequestration or explain regional discrepancies in nutrient and new production mass balances (*2*, *10*, *11*, *28*). Whether these speculations are reasonable for tropical and subtropical waters depends on the extent to which they incorporate community structure or production enhancement of export ratios and the temporal and spatial scales being considered. Here, the eventual decay of Cyclone Opal would have relaxed uplifted isopycnal surfaces and moved downward any unused nutrients and accumulated organic matter within







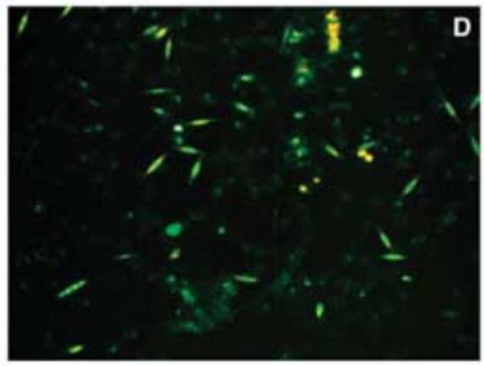


Fig. 3. Diatom biomass in the DCM. (**A**) Diatom biomass versus depth (μg C l^{-1}) during the decline of a diatom bloom; $t = 0$ (solid circles) denotes the first sampling of the bloom. Repeated samplings on days 3 and 8 after the initial encounter depicted by solid squares and diamonds, respectively. For comparison, the OUT station is also shown (crosses). (**B**) An epifluorescent image of the phytoplankton population within the DCM at the OUT station. (**C** and **D**) Epifluorescent images of the phytoplankton population within the DCM at the center of Cyclone Opal during the initial sampling [$t = 0$ day (C)] and 8 days later [$t = 8$ days (D)] during the bloom decline. Images were taken of slides viewed at 200× magnification, and each image represents >8 μm cells from 500 ml of preserved seawater (*9*). The red color reflects chlorophyll autofluorescence. Note the transition in diatom species from large centric genera (*Rhizosolenia* and *Chaetoceros*) to smaller genera (for example, *Mastogloia*).

those density layers from lighted surface waters. Thus, elemental constituents locked into eddies by efficient remineralization are exported but not effectively sequestered on annual time scales, because they reside immediately below the euphotic zone. Nonetheless, if eddies function as selective silica pumps (*1*-*4*), these sub-euphotic waters will be disproportionately depleted in silicic acid. To the extent that Si-limitation modulates diatom growth and biomass accumulation, one long-term consequence of repeated nutrient entrainment by wind-driven eddies may be to reduce diatom response, further complicating explanations of how these features affect open-ocean biogeochemistry.

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Supporting Online Material

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Materials and Methods
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Eddy/Wind Interactions Stimulate Extraordinary Mid-Ocean Plankton Blooms

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Episodic eddy-driven upwelling may supply a significant fraction of the nutrients required to sustain primary productivity of the subtropical ocean. New observations in the northwest Atlantic reveal that, although plankton blooms occur in both cyclones and mode-water eddies, the biological responses differ. Mode-water eddies can generate extraordinary diatom biomass and primary production at depth, relative to the time series near Bermuda. These blooms are sustained by eddy/wind interactions, which amplify the eddy-induced upwelling. In contrast, eddy/wind interactions dampen eddy-induced upwelling in cyclones. Carbon export inferred from oxygen anomalies in eddy cores is one to three times as much as annual new production for the region.

Understanding the controls on primary production in the upper ocean is of fundamental importance for two main reasons. First, primary productivity sets a first-order constraint on the energy available to sustain oceanic ecosystems. Second, fixation and subsequent sinking of organic particles remove carbon from the surface ocean (the so-called biological

pump), which plays a key role in the partitioning of carbon dioxide between the ocean and atmosphere. Geochemical estimates of new production (*1*) surpass the apparent rate of nutrient supply by vertical mixing by a factor of 2 or more in subtropical oceans (*2*–*6*), which constitute some of the largest biomes on Earth. Two possible mechanisms to supply the "missing" nutrients locally include nitrogen fixation by cyanobacteria (*7*–*10*) and intermittent upwelling by mesoscale eddies and submesoscale processes (*11*–*21*).

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There are at least three types of mid-ocean eddies in the northwestern subtropical Atlantic: cyclones, anticyclones, and mode-water eddies (Fig. 1A). Cyclones dome both the seasonal and main pycnoclines, whereas regular anticyclones depress both density interfaces. Mode-water eddies derive their name from the thick lens of water that deepens the main pycnocline while shoaling the seasonal pycnocline. Because the geostrophic velocities are dominated by depression of the main pycnocline, the direction of rotation in mode-water eddies is the same as in regular anticyclones. However, displacement of the seasonal pycnocline is the same as in cyclones: Both types of features tend to upwell nutrients into the euphotic zone during their formation and intensification phases. As these eddies spin down, the density surfaces relax back to their mean positions, and thus decaying cyclones and mode-water eddies will have downwelling in their interiors. This temporal evolution during the life cycle of an eddy is a key regulator of the biogeochemical response (*22*, *23*).

Eddy features are readily discernible via satellite altimetry (Fig. 1B and fig. S1). Access to these data in near-real time (*24*) facilitates the tracking of individual eddies and adaptive sampling in shipboard operations. In 2004 and 2005, we sampled a total of 10 different eddies, 5 more than once (table S1). Time series within target features allow the resolution of temporal dynamics in eddy-driven nutrient supply, phytoplankton physiological response, changes in community structure, and biogeochemical fluxes. We focus this discussion on cyclone C1 and mode-water eddy A4; findings in other cyclones and mode-water eddies in this study (table S1) as well as prior investigations (table S2) are consistent with those presented here.

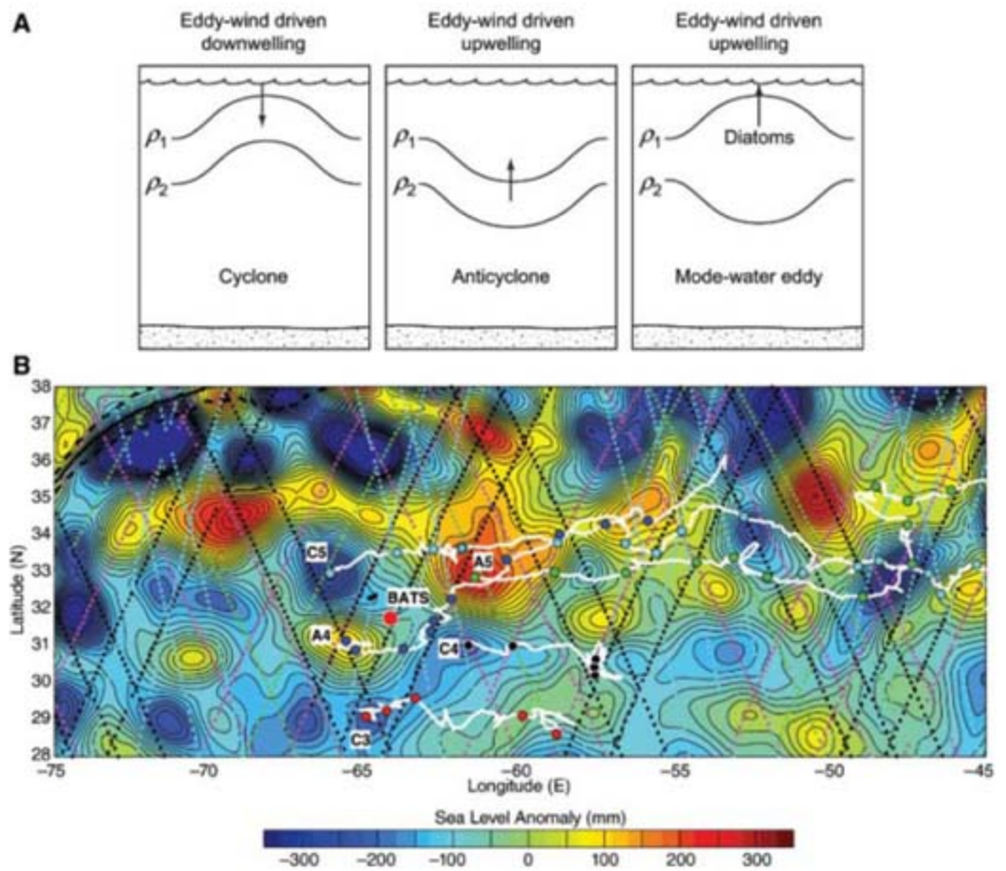


Fig. 1. (**A**) Isopycnal displacements associated with three types of eddies. Two density surfaces are depicted: one in the seasonal thermocline ρ_1 and one in the main thermocline ρ_2. Arrows indicate the sense of the vertical velocity arising from the interaction of the wind with the underlying eddy-driven flow, which is upward in anticyclones and mode-water eddies and downward in cyclones. This eddy/wind interaction stimulates diatom blooms in mode-water eddies. (**B**) Objective analysis of SLA for 17 June 2005, just before the first cruise of the 2005 field season. The Gulf Stream mean path and meander envelope (1 SD) are indicated as solid and dashed black lines, respectively. Prior trajectories of the features of interest are indicated by white lines emanating from eddy centers, with dots at 30-day intervals. Satellite ground tracks are shown for the Jason (magenta), Topex 2 (green), Geosat Follow-on (black), and European Remote Sensing/Envisat (light blue) satellites. A corresponding map for the 2004 field season is provided in fig. S1.

Cyclone C1 was occupied by ships four times between June and August 2004 (*25*). Shipboard acoustic Doppler current profiler (ADCP) data documented the counterclockwise flow associated with C1's negative sea-level anomaly (SLA), and its altimetric history suggested intensification in May. Uplift of near-surface isopycnals was associated with shoaling and enhancement of the subsurface chlorophyll maximum. The magnitude of the subsurface chlorophyll maximum in C1 was lower than in other cyclones (Fig. 2A), yet still in the upper quartile of all subsurface maxima observed in the Bermuda Atlantic Time-series Study (BATS) (*26*) from 1988 to 2003.

Phytoplankton species composition in cyclone C1 resembled mean conditions at the BATS site (Fig. 2B). On average, *Prochlorococcus* spp., *Synechococcus* spp., pelagophytes, and prymnesiophytes constitute the largest fractions of total chlorophyll a in the depth interval from 75 to 140 m (deep chlorophyll maximum) at the BATS site; diatoms, dinoflagellates, and prasinophytes contribute comparatively little to total chlorophyll a. The eddy-induced bloom in C1 increased the relative amount of *Prochlorococcus* spp. and decreased the relative amount of *Synechococcus* spp., and the rare groups constituted an even smaller fraction of total chlorophyll a.

In subsequent occupations of cyclone C1, conditions at the eddy center changed from a local maximum to a local minimum in chlorophyll a and fluorescence. During this latter phase, integrated primary production at the eddy center was not statistically distinguishable from climatological summertime conditions at the BATS site, nor were bacterial production and biomass (table S3). However, systematic mesoscale variability was observed in microbial parameters, with biomass and production enhancement at the periphery relative to the eddy center. Zooplankton biomass was also elevated on the periphery relative to the eddy center, with large zooplankton migrators (>5 mm) increasing most. Although zooplankton biomass was not significantly different from the long-term BATS summertime mean (1994–2005), there was significant enhancement [analysis of variance (ANOVA), $P < 0.05$] above mean summertime conditions for 2004–2005 (table S3).

Export measured with drifting sediment traps was below the BATS summertime mean, al-

though not anomalously so, given the variability at the BATS site (table S3). ^{234}Th-based export fluxes were consistent with these findings (table S3). However, subsurface oxygen distributions suggest a substantial export event before our observations. During the first occupation, cyclone C1 contained an oxygen minimum in the depth interval from 200 to 400 m (*27*), in which the oxygen concentrations were lower than all previous measurements at the BATS site in that stratum (Fig. 2C). Nitrate and dissolved inorganic carbon were also enhanced in the feature, in approximately Redfield proportion with the oxygen anomaly. One month later, the magnitude of the oxygen anomaly had decreased by 50% (Fig. 2C). Thus, the oxygen deficit appears to be an ephemeral feature, with a time scale shorter than the lifetime of the eddy.

An estimate of remineralization implied by the oxygen deficit can be computed from differences in oxygen inventories inside versus outside the eddy in this depth interval (Fig. 2C) (*28*). Using photosynthetic stoichiometry of 138 O_2:106 C:16 N:1 P, remineralization is 1.4 mol of N m^{-2}, which is approximately three times the annual new production for the region (*3*). Water mass analysis suggests that the eddy core may have had a distant origin in the southern Sargasso Sea. Using biogeochemical characteristics of the distant waters as the background from which the anomaly is computed, the implied remineralization is 0.7 ± 0.2 mol of N m^{-2}, which is approximately 1.4 times the annual new production at the BATS site.

Mode-water eddy A4 was occupied six times between June and September 2005. Its SLA was positive (Fig. 1B), and shipboard ADCP measurements confirmed anticyclonic flow. Its altimetric history suggested a relatively persistent SLA of 20 cm for the 4 months preceding our first occupation.

High-resolution surveys with a towed undulating Video Plankton Recorder (*29*) revealed an extraordinary phytoplankton bloom in the interior of A4 (Fig. 3A). Although submesoscale variability was evident, the enhancement spanned the eddy's inner core (*30*). Peak chlorophyll a measured near the eddy center was 1.4 μg of chlorophyll a $liter^{-1}$, eclipsing the highest value ever measured at the BATS site by a considerable margin (Fig. 2A). This measurement is 8 SD above the mean subsurface maximum at the BATS site.

Phytoplankton species composition in mode-water eddy A4 departed dramatically from mean

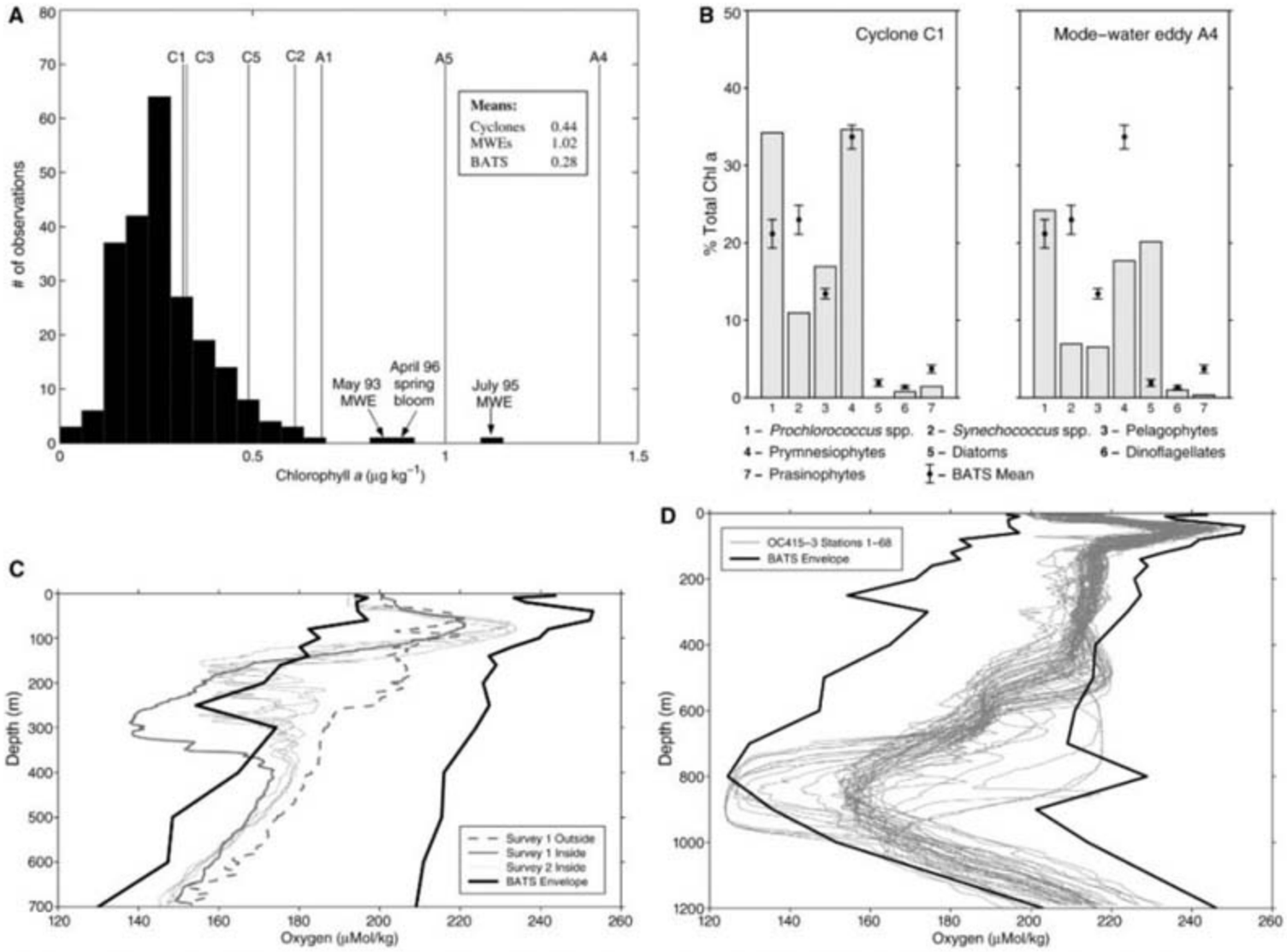
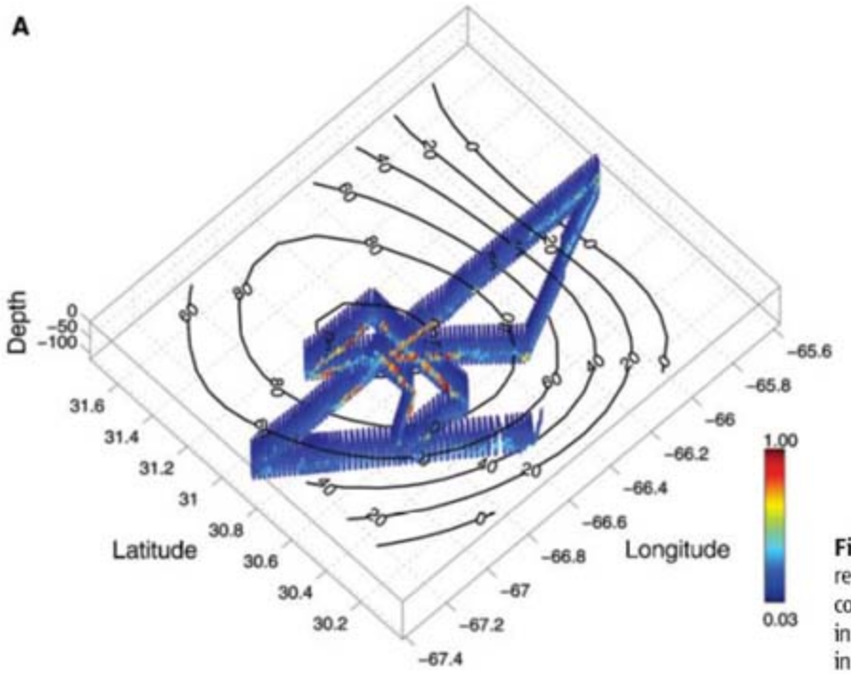


Fig. 2. (**A**) Histogram of subsurface maxima in chlorophyll a from BATS data from 1998 to 2003. Peak chlorophyll a values in cyclones (C1, C2, C3, and C5) and mode-water eddies (A1, A4, and A5) from the present observations (table S1) are indicated by thin vertical lines. (Inset) Means of the peak chlorophyll a concentrations (micrograms per kilogram) in cyclones and mode-water eddies (MWEs) from the present observations, compared to the mean subsurface maximum from BATS. (**B**) Phytoplankton species composition (at the depth interval from 75 to 140 m) in cyclone C1 (OC404-1 station 18) and mode-water eddy A4 (OC415-1 station 16). Estimates of the relative abundance (by pigment mass) of seven different groups, expressed as the percentage of total chlorophyll (Chl) a, were calculated from high-performance liquid chromatography pigment data together with the algorithms described in (*53*). Means and associated 95% confidence intervals for each group, derived from the BATS data for 1989–2003, are indicated in both plots. (**C** and **D**) Oxygen profiles in cyclone C1 (C) and mode-water eddy A4 (D). The envelope of BATS measurements from 1988 to 2003 is indicated by bold lines.

conditions at the BATS site (Fig. 2B), expressed primarily in a shift toward a diatom-dominated community (*31*). The amount of chlorophyll a in diatoms in A4 was 8 SD above the BATS mean. Shipboard microscopic cell counts from a sample in the high-chlorophyll region indicated ~8000 colonies liter^{-1} of the chain-forming diatom *Chaetoceros* spp. Given that each colony contained ~15 cells, we estimate the diatom



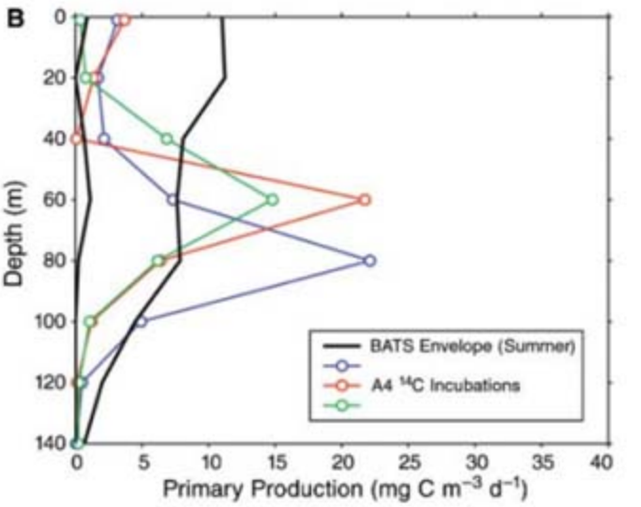


Fig. 3. (**A**) Three-dimensional distribution of chlorophyll a fluorescence (in relative units) from a Video Plankton Recorder survey of A4, overlayed on contours of SLA (in millimeters) from objectively analyzed satellite data as in Fig. 1B. (**B**) ^{14}C primary production profiles inside mode-water eddy A4 in August 2005. The minimum and maximum of BATS summertime observations from 1988 to 2003 are indicated by thick black lines.

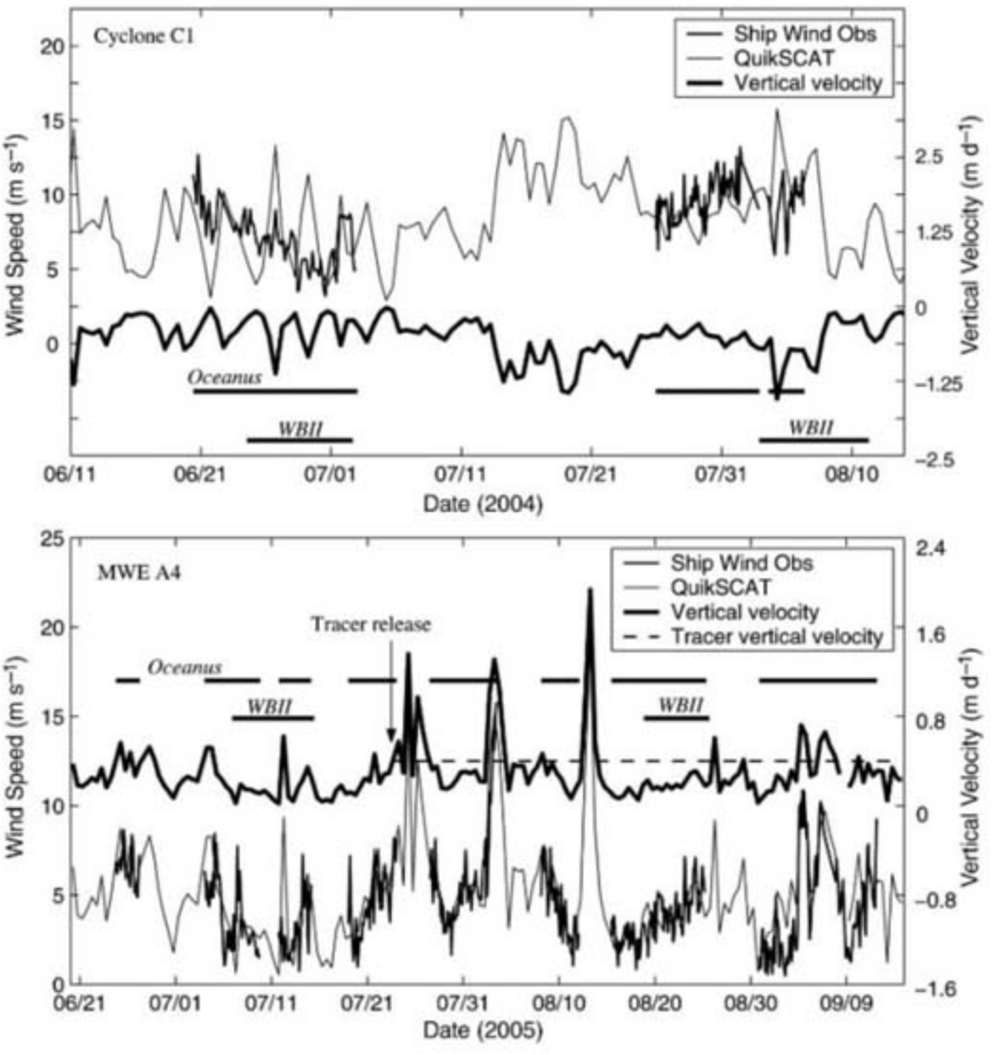


Fig. 4. Winds and computed vertical velocities arising from wind/eddy interactions in cyclone C1 (**top**) and mode-water eddy A4 (**bottom**). Satellite-based wind measurements along the eddy trajectories (determined by satellite altimetry and shipboard observations) were obtained from QuikSCAT level-3 data, available on a 0.25° twice-daily global grid (see http://podaac.jpl.nasa.gov/quikscat/). Time periods of ship occupations by R/V *Oceanus* and R/V *Weatherbird II* (*WBII*) are indicated by horizontal bars. Shipboard wind observations (R/V *Oceanus*) reveal excellent agreement with the satellite-based measurements. Vertical velocities at the eddy center were computed with the formulas of Martin and Richards (*40*), assuming a spatially uniform wind over the eddy. The use of a spatially variable wind introduces additional high-frequency fluctuations in vertical velocity, but their impact on the mean is less than 10%. Vertical velocity estimated from a sulfur hexafluoride tracer release in mode-water eddy A4 (0.4 m day^{-1}) for the time period between the release and the final survey is indicated by a dashed line in the lower panel.

concentration to have been four to five orders of magnitude above the background concentration of 1 to 10 cells liter^{-1}. The propensity of mode-water eddies to form diatom blooms emerges as a systematic aspect of these data (table S1) and prior observations (table S2): The three highest chlorophyll a values in the present data and two of the three highest values in the BATS time series (*22*, *32*) (Fig. 2A) were all associated with diatom-dominated phytoplankton communities in mode-water eddies (*33*).

In the first occupation of mode-water eddy A4, primary production was not significantly different from mean summertime conditions at the BATS site. In the second occupation, primary production was significantly enhanced (table S3) (*34*). The primary production anomaly had an unusual vertical structure, with a subsurface maximum that exceeded the envelope of BATS observations in the depth interval from 60 to 80 m (Fig. 3B). This structure is consistent with enhanced nutrient supply from below and a diatom population capable of high growth rates in low-light conditions (*35*, *36*).

Zooplankton biomass at the eddy center varied more than threefold (table S3). Maximum vertically integrated biomass occurred at the same location as the anomalously high primary production (Fig. 3B), with the largest increase in the 1- to 5-mm size range. Zooplankton biomass in A4 was higher than in 2004–2005 BATS summer samples but not significantly different (ANOVA, $P > 0.05$) from the long-term BATS summer mean (table S3). However, samples from cyclones and mode-water eddies constitute 6 of the top 10 highest zooplankton biomass observations in the combined data set.

Export measured in A4 was below the BATS summertime mean, although within the range of variability observed at the BATS site (table S3). ^{234}Th-based export flux estimates yielded similar values (table S3). The bloom in A4 was accompanied by exceptionally low oxygen concentrations (~120 μmol kg^{-1}) in the depth interval from 800 to 1000 m (Fig. 2D), which is lower than ever measured at the BATS site. Remineralization implied by the difference between the observed oxygen deficit inside the eddy and background conditions outside the eddy was 0.8 mol of N m^{-2} (*28*), which is ~1.6 times the annual new production for the region. As in cyclone C1, the oxygen deficit coincided with a discernible salinity anomaly, suggesting that the water mass may have had a distant origin. The climatological salinity distribution (*37*) indicates potential origins along the northern and southern limbs of the subtropical gyre. The latter contains oxygen concentrations comparable to that observed in the core of A4, whereas the former contains much more oxygen. Thus, the southern source region implies that the oxygen deficit is primarily an advective feature, whereas the northern source region requires a substantial eddy-induced export event (*38*).

Why is the biological response to cyclones and mode-water eddies so different? Macronutrient stoichiometries just below the euphotic zone are similar (*39*), suggesting a physical cause. We hypothesize that the difference arises from asymmetry in vertical motions induced by eddy/wind interactions. To quantify this effect, we used a model of uniform wind blowing over an idealized anticyclonic vortex, with wind stress formulated as the difference between air and water velocities at the sea surface (*40*). Stress is enhanced on the flank of the eddy where wind and current oppose each other, and stress is reduced on the flank where they flow in the same direction. This generates a divergence in the center of an anticyclone regardless of wind direction. Applying this model to A4, the upwelling velocity induced by the eddy/wind interaction ranges from 0.1 to 1.6 m day^{-1} (Fig. 4) (*41*). Upward motion in the interior of A4 was confirmed by a tracer release experiment, during which the tracer moved upward at 0.4 m day^{-1}, almost exactly the rate predicted from the eddy/wind interaction model (Fig. 4).

The eddy/wind interaction model predicts downwelling in the interior of cyclone C1 (Fig. 4). The low biomass and productivity at the eddy center during the latter stages of our observations are consistent with the predicted eddy/wind-induced downwelling. Unfortunately, there was no tracer release in C1 that can be used to test this prediction. Nevertheless, it is clear that eddy/wind interactions enhance the vertical nutrient flux in mode-water eddies, and they counterbalance it in cyclones (Fig. 1A). This may explain why phytoplankton enhancement in cyclones is rather ephemeral, whereas mode-water eddies can produce long-lasting blooms of diatoms (*42*).

Observations presented here document eddy-driven events that exceeded the envelope of variability in prior measurements of chlorophyll a, primary productivity at depth, and oxygen in a particularly well-studied region of the world ocean. Episodic phenomena continue to be undersampled in extant oceanographic databases, and the prospects for capturing them in traditional time-series mode are statistically humbling (*43*). More complete assessment of the influence of eddies on biogeochemical cycling will require models that fully resolve these processes. Existing models differ in this regard, some indicating little integrated impact (*44*) and others suggesting that eddies are the dominant mechanism of nutrient supply in the interior of the subtropical gyre (*45*). Improved estimates will require a number of revisions to prior models so that different responses in cyclones and mode-water eddies can be resolved. These include explicit representations of eddy/wind interactions and mechanistic links between mesoscale dynamics, species composition, and export.

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30. The small-scale (on the order of 10 km) fluorescence patchiness observed in the Video Plankton Recorder survey (Fig. 3A) is reminiscent of submesoscale frontal phenomena present in high-resolution numerical simulations (*14*, *15*, *19*, *21*). Details of the relationship between, and interactions among, submesoscale and mesoscale processes remain a topic of active research. The key aspect of the observed fluorescence distribution as it pertains to diagnosis of the underlying mechanism is that the enhancement resides at the eddy center, not at the periphery.
31. Picophytoplankton concentrations determined by flow cytometry showed no significant difference in standing stocks of *Prochlorococcus* spp. or *Synechococcus* spp. between A4 and C1, although their relative contribution to total chlorophyll a decreased significantly in A4 because of the large diatom bloom (Fig. 2B).
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34. Depth-integrated bacterioplankton biomass and production were not significantly different from the long-term mean at the BATS site. However, as compared to C1, volumetric bacterioplankton biomass and production in A4 were significantly enhanced within the deep chlorophyll a maximum, where diatoms dominated.
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39. Nitrate-to-silicate ratios were similar in cyclone C1 and mode-water eddy A4. Concentrations in the upper euphotic zone were consistent with nitrogen limitation, because excess silicate (~1 to 2 μmol kg^{-1}) was present in waters in which nitrate was depleted (<0.1 μmol kg^{-1}). All of the eddies we studied exhibited a similar tendency for the phosphocline to reside deeper than the nitracline, leading to supra-Redfield nitrate:phosphate ratios just below the euphotic zone. This enigmatic aspect is characteristic of the region (*49*, *50*). Nevertheless, we could find no systematic differences in nitrate-to-phosphate ratios between cyclones and mode-water eddies.
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41. The Martin and Richards model (*40*) predicts the vertical velocity at the base of the layer through which wind stress can be transmitted directly through waves and turbulence (the Ekman layer). Quasigeostrophic theory and models demonstrate that this vertical motion penetrates well into the inviscid interior, diminishing with depth (*51*). We ran a primitive equation model simulation of eddy A4, which indicated that the vertical velocity at the depth of the high-chlorophyll layer was ~90% of the Ekman upwelling velocity. The physical manifestation of this effect is a tendency for upward displacement of the seasonal pycnocline at the eddy center, enhancing the mode-water eddy structure (Fig. 1A).
42. This model also predicts upwelling in the interior of regular anticyclones. An analogous phenomenon has been hypothesized to upwell depressed density surfaces in the interiors of warm-core Gulf Stream rings (*51*), a process that would tend to enhance biological activity associated with their frictional decay (*52*).
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54. We thank the officers and crews of the R/V *Oceanus* and R/V *Weatherbird II* for their outstanding support during our seagoing operations. R. Leben provided near–real-time altimetric data that were crucial for our adaptive sampling effort. Nutrient samples were processed by the Nutrient Analytical Facility (P. Henderson) at the Woods Hole Oceanographic Institution. Numerical simulations were performed at the National Center for Atmospheric Research's Scientific Computing Division. We thank O. Kosnyreva for expert data analysis and visualization and S. Stasiowski for administrative support. We gratefully acknowledge the efforts of all participants in the EDDIES project, which included a number of BATS technicians. For more information, see http://science.whoi.edu/users/olga/eddies/EDDIES_Project.html. The EDDIES project was funded by NSF's Chemical, Biological, and Physical Oceanography Programs. Additional support for remote sensing aspects (including altimetry and QuikSCAT wind analyses) and high-performance liquid chromatography pigment assays (C. Trees, Center for Hydro-Optics and Remote Sensing) was provided by NASA.

Supporting Online Material

www.sciencemag.org/cgi/content/full/316/5827/1021/DC1
Materials and Methods
Fig. S1
Tables S1 to S3
References

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Stress Control of Deep Rift Intrusion at Mauna Loa Volcano, Hawaii

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Mauna Loa volcano, Hawaii, deforms by a combination of shallow dike intrusions in the rift zones and earthquakes along the base of the volcano, but it is not known how the spreading is accommodated in the lower part of the volcanic edifice. We present evidence from interferometric synthetic aperture radar data for secular inflation of a dike-like magma body at intermediate depth in the southwest rift zone during 2002 to 2005. Magma accumulation occurred in a section of the rift zone that was unclamped by previous dikes and earthquakes, suggesting that stress transfer plays an important role in controlling subsurface magma accumulation.

Modern volcano-monitoring techniques can detect precursory seismic unrest months to days before an eruption, but information about possible eruption locations is generally not available. Such information is important for hazard assessment and for timely warning of the population for large and populated basaltic shield volcanoes such as Mauna Loa volcano in Hawaii. Forecasting the eruption location requires a better understanding of subsurface magma migration. Here we show that the 2002 to 2005 magma intrusion at Mauna Loa volcano inferred from space-geodetic data is consistent with changes in the stress due to the previous tectonic and magmatic events. This suggests that the stress field within the volcanic edifice is a dominant effect in controlling magma accumulation. Space-geodetic measurements can be used to infer changes to the stress field in the interior and contribute to better forecasts of the response of a volcano to the arrival of new magma from below.

Mauna Loa volcano is the largest and one of the most active volcanoes on Earth. It has produced more than 4 km^3 of lava during the past 150 years (*1*). Most historic eruptions involved the propagation of an eruptive fissure from the summit downrift into the northeast rift zone (NERZ) or into the southwest rift zone (SWRZ) (Fig. 1A). About 30 to 40% of the volcano's subaereal surface has been covered by new lava during the past 1000 years. Thus, a large portion of the island is threatened by lava flows, and it is very important to better estimate where possible eruptions could occur. The last major eruptions occurred in 1950 from the SWRZ and in 1984 from the NERZ. At Mauna Loa, repeated dike intrusions into the rift zone result in seaward motion of the volcano flanks, most of which is believed to be accommodated in form of seismic or aseismic displacement along a decollement fault on the paleo-seafloor at the base of the volcanic edifice at 12- to 14-km depth below the summit. The 1868 magnitude (M) 8 Pahala (*2*) and the 1951 M6.9 Kona earthquakes (*3*) likely ruptured the decollement.

Inflation at Mauna Loa volcano started in May 2002 at the same time when Kilauea volcano increased its rate of lava production (*4*). Subcrustal seismicity increased in 2004 (Fig. 1A). We used interferometric synthetic aperture radar (InSAR) acquired by the Canadian Radarsat-1 satellite between 2001 and early 2006 to obtain a detailed image of the ground deformation associated with the volcanic inflation. InSAR measures the change in distance between the ground and the satellite in radar line-of-sight (LOS) direction. We used imagery with different incidence angles of the radar beam and an average of five to nine interferograms each spanning 3 to 4 years for each viewing geometry (table S1) to obtain averaged LOS velocities for the period May 2002 to end 2005 (*5*). Averaging interferograms increases the signal-to-noise

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ratio of the measurements, which are affected by path delays in the troposphere and by uncertainties in the satellite orbits. InSAR in Hawaii is challenging because repeating weather patterns and up to 4200 m of topography can cause phase contributions of several cycles. Combining multiple viewing geometries better constrains the deformation sources and allows one to estimate the vertical and east component of the velocity field (*6*).

The interferograms show a distinct pattern of ground deformation in the summit area and on the upper flanks of Mauna Loa. For an east-looking interferogram (Fig. 1A), a roughly circular area with a diameter of 10 km west of the rift zone moves toward the radar with a velocity of more than 1 cm/year and maximum velocity of 5 cm/year (yellow-red colors). A smaller area on the southeast flank is moving away from the radar (blue colors). The vertical velocity field is characterized by two lobes of uplift of up to 6 cm/year on either side of the SWRZ, and the east velocity field is roughly symmetric across the SWRZ (Fig. 1B). The symmetry of the ground-velocity field clearly indicates that the principal source of deformation is located within the rift zone.

To understand what causes the observed deformation, we assume elastic material behavior and use geophysical inverse-modeling methods. We first test simple, kinematic models consisting of point (Mogi) sources of inflation and uniform opening dislocations. We find that the data are well explained using a model with a Mogi source southeast of the caldera and an opening dislocation bisecting the caldera and upper SWRZ (*7*). We then consider a more realistic, mechanical model with the magma chamber and dike hydraulically connected and sharing the same excess magma pressure (*8*). The magma chamber is represented as a finite, spherical cavity (*9*) and the dike as a gridlike combination of 1 km by 1 km opening dislocation elements covering 30 km of the rift zone from the surface to the decollement at 14-km depth, subject to a uniform excess-pressure boundary condition. The effect of topography is included in the model (*10*). We invert simultaneously for the opening status of the individual dislocation elements on the dike plane (open or closed) (*11*), for the excess magma pressure, for the location and radius of the spherical cavity, and for phase ramps for each averaged interferogram to account for orbital uncertainties using a Monte Carlo–type simulated annealing algorithm (*12*). The actual opening distribution of the dike-like magma body depends on the configuration of connected dislocation elements.

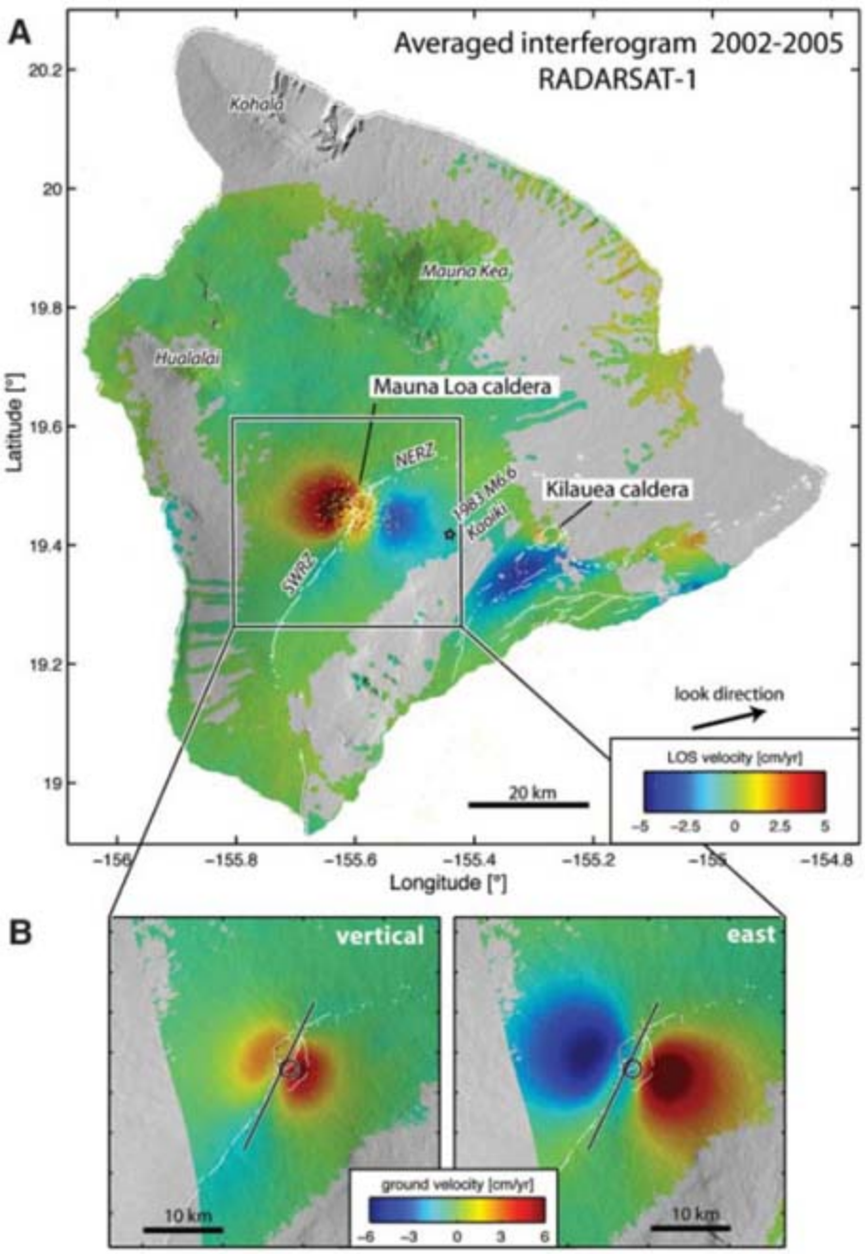

Fig. 1. (**A**) Averaged 2002 to 2005 satellite radar interferogram of the Big Island of Hawaii showing ground velocity in the radar line-of-sight (LOS) direction. The radar looks toward the east (ascending orbit) with an incidence angle of ~45° on the ground (Standard Beam A6). The star denotes the 1983 Kaoiki earthquake. The seismicity with depth > 20 km and with $M > 2.2$ is also shown. (**B**) Vertical and east component of the ground-velocity field obtained by combining averaged interferograms from four different viewing geometries. The black line and circle indicate the dike and magma chamber, respectively, of the model in Fig. 2A.

We find that the model magma chamber is under the southeastern caldera margin at 4.7-km depth below the summit (at 0.5-km below sea level) (Fig. 2A); this was also the inferred location of the active reservoir during the 1984 eruption (*13*). The radius of the magma chamber is 1.1 km and the rate of magma excess pressure increase is 1.8 MPa/year. Most of the dike inflation occurs at 4- to 8-km depth along an 8-km-long zone, resulting in an opening of 0.2 to 0.35 m/year (*14*). This model explains about 96% of the data variance. Comparison of the data with the model predictions shows that the data fit is generally very good except near the summit (Fig. 2B). The differences arise because of simplified model assumptions such as a spherical magma chamber and uniform elastic parameters (*15*) and because we did not account for the subtle, pre-2002 subsidence of the summit area detected with the Global Positioning System (*16*) and for the subsidence of the recent intracaldera lava flows due to cooling. We do not include possible fault slip under the flanks because the geometry of the fault plane and the amount of slip are not well constrained (*17*). Other model simplifications are that the dike opening is constrained to take place within the volcanic edifice (to a depth of 14 km below the summit) and that horizontal and vertical variations in the magma pressure go along with variations in the tectonic stress field so that the magma excess pressure is constant.

Although details of the opening distribution of the dike should be interpreted with caution, we conclude that about 80% of the magmatic intrusion occurs in the intermediate and deep section of the rift zone at depth larger than the shallow magma reservoir. This suggests that the volcano operates in a manner similar to that inferred for its neighbor Kilauea with secular magma intrusion into the deep section of the rift zone and occasional dike injection into the shallow section (*18*). Indeed, the intrusion of magma into the deep section of the rift

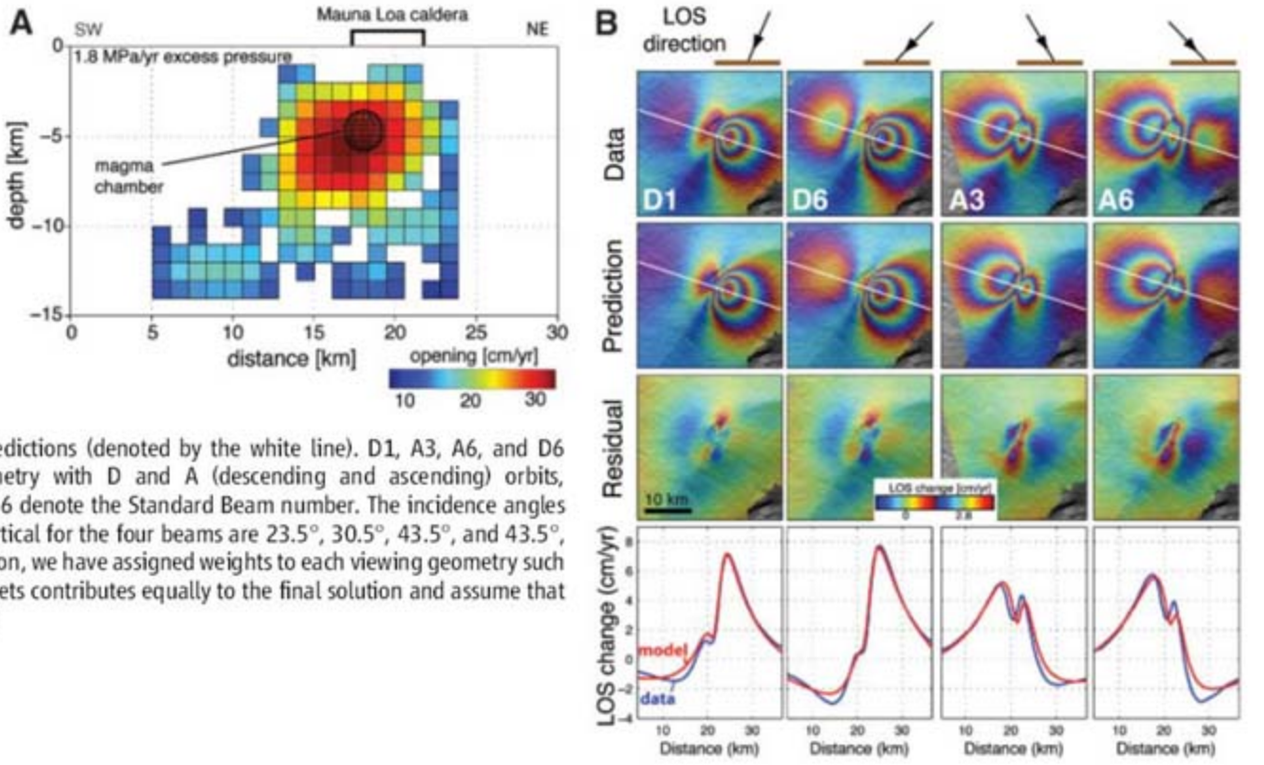

Fig. 2. (**A**) Opening of Mauna Loa's riftzone inferred by inversion of the interferometric data based on a uniform excess–magma pressure model. For the horizontal location of the cross section and magma chamber, see Fig. 1B. (**B**) LOS direction, data, model predictions, residual between data and model prediction, and rift–perpendicular profile of data and model predictions (denoted by the white line). D1, A3, A6, and D6 denote the viewing geometry with D and A (descending and ascending) orbits, respectively, and 1, 3, and 6 denote the Standard Beam number. The incidence angles on the ground from the vertical for the four beams are 23.5°, 30.5°, 43.5°, and 43.5°, respectively. For the inversion, we have assigned weights to each viewing geometry such that each of the four data sets contributes equally to the final solution and assume that the data are uncorrelated.

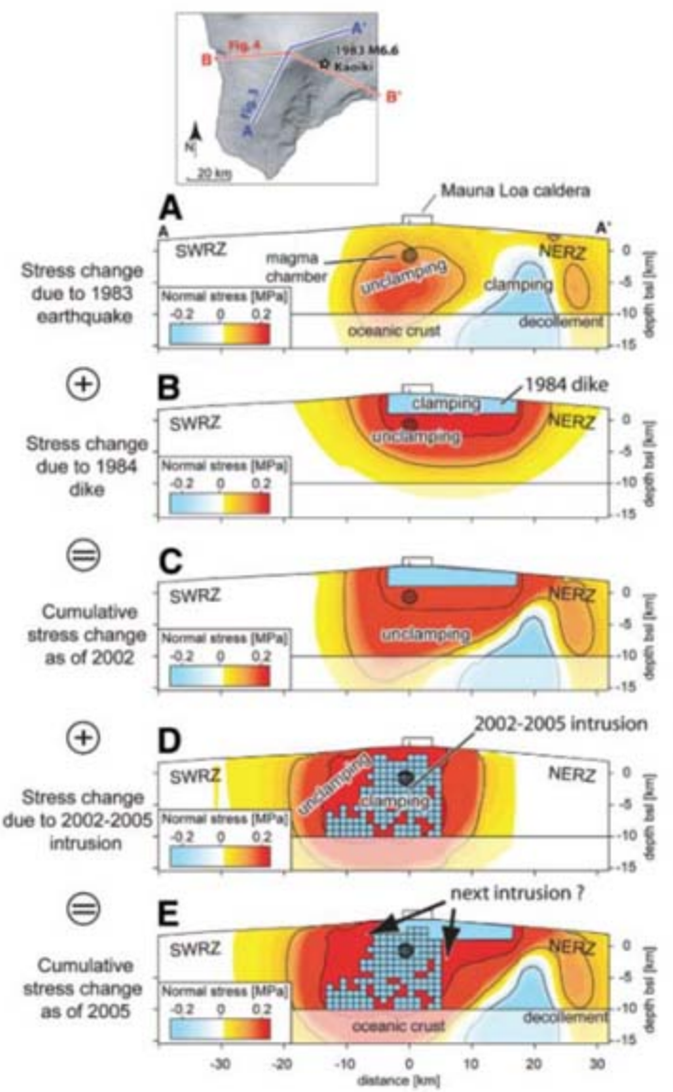

Fig. 3. Changes in normal stress along Mauna Loa's rift zone due to (**A**) the 1983 *M*6.6 Kaoiki earthquake, (**B**) the dike associated with the 1984 eruption, and (**D**) the 2002 to 2005 rift intrusion. (**C** and **E**) The sum of the stress changes from (A) and (B) and (A), (B), and (D), respectively. The color scale is saturated at ±0.2 MPa. Solid lines denote ±0.1 and ±1 MPa contours. The 2002 to 2005 dike intrusion occurs in the area of greatest unclamping. The stress change is resolved in the direction normal to the overall strike of the SWRZ and NERZ along AA′ (see inset). We simulate the earthquake by 0.35 m of strike- and dip-slip displacement along the 225-km^2 fault surface (fig. S3). For the 1984 dike, we use a depth extension of 3 km. This is more than modern, space-geodetic estimates of 1 to 2 km for dikes at Kilauea (*29*), in the Galapagos Islands (*30*), and Piton de la Fournaise (*31*) but less than the estimate of (*13*), which we do not consider reliable because it is based on very few tilt and leveling measurements. It ensures that the dike is well above the magma chamber.

zone is required from simple geometric considerations because all known dike intrusions occurred within the shallow section to a depth of less than 5 km (*19*). The inferred rate of magma accumulation of 21 × 10^6 m^3/year is almost three times the long-term growth rate averaged over the past 4000 years (*19*). As magma intrusion is continuing as of March 2007, albeit at a lower rate, there are no indications that Mauna Loa's magma production rate is waning, as suggested by the decreased eruption rate over the past 50 years (*20*).

We discuss whether the spatial pattern of magma intrusion can be explained by stress transfer and how the 2002 to 2005 intrusion changed the stress field in the interior of the volcano. We first consider changes in the ambient normal stress along the rift zone. We would expect magma intrusion in sections of the rift zone for which the normal stress change resulted in unclamping (positive normal stress change) but no intrusion in clamped sections of the rift zone (negative stress change) (*21*, *22*).

The largest events during the past 25 years were a *M*6.6 earthquake in 1983 and the eruption from the NERZ in 1984. The earthquake occurred in the Kaoiki seismic zone 15 km southeast of the summit (Fig. 1A) and involved right-lateral strike-slip and seaward decollement faulting (*23*). The eruption was associated with a dike propagating from the summit a few kilometers into the SWRZ zone and then into the NERZ from where most of the lava erupted (*1*).

The 1983 earthquake unclamped the upper SWRZ, the upper NERZ, and a section of the NERZ further down the rift (Fig. 3A) (see supporting online material). The 1984 dike unclamped large parts of the rift zone but clamped the section in which it intruded (Fig. 3B). The dike likely relieved stress due to prior events, which is not

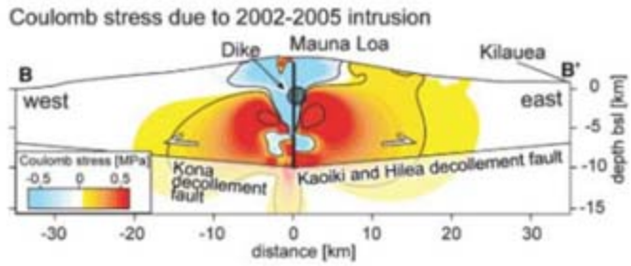

Fig. 4. Changes in Coulomb failure stress resolved for seaward motion parallel to BB′ (see Fig. 3 inset) along 5° inward-dipping faults in a cross section perpendicular to the rift zone. The color scale saturates at ±0.5 MPa. Contours are as in Fig. 3.

included in this stress-change budget. Together, the earthquake and the dike unclamped most of the rift zone (Fig. 3C), with the largest unclamping (by more than 0.2 MPa) occurring in the southern summit section at a depth of 2 to 6 km (the area of inferred magma intrusion during 2002 to 2005).

The 2002 to 2005 intrusion unclamped the rift zone, except in the area of magma intrusion (Fig. 3D). The magnitude of stress change is similar to that for the 1984 dike (Fig. 3B). The inferred opening rate corresponds in places to an opening of 1 m during the 3.3 years covered by our data, even larger in thickness than the 1984 dike. The stress change since 1983 is given by the sum of the stress changes due to the 1983 earthquake, the 1984 dike, and the 2002 to 2005 intrusion (Fig. 3E). The unclamping is most pronounced in the shallow section of the upper SWRZ and in the intermediate-depth section of the NERZ.

The stress-change modeling shows that the magma intrusion during 2002 to 2005 occurred into the most-unclamped section of the rift zone since 1983 (*24*). This observation is notable because it suggests that the stress changes due to the 1983 and 1984 events influenced, if not controlled, the accumulation of the magma. Consequently, if we can constrain the deformation sources to reliably estimate changes in the stress field, we can forecast the location for the accumulation of new magma and possibly of eruptions based on the stress-change models. Obviously, other factors also contribute, such as local stress heterogeneities associated with the magma conduits and magmatic factors such as the size and compressibility of the reservoir feeding the intrusion and the vesicularity and density of the magma, but our results suggest that stress changes due to prior events are the dominant effect.

The historic eruptions of Mauna Loa were fissure eruptions associated with dikes injected into the shallow rift zone. After the 2002 to 2005 intrusion, the most favorable stress conditions for the propagation of shallow dikes occurred in the upper SWRZ (Fig. 3E). Thus, according to the stress-change models, this is the most likely location for a new dike injection and possibly for an eruption. The last eruption from this section of the rift zone occurred in 1950. A new eruption from the SWRZ would be consistent with the previously observed pattern of alternating eruptions between the NERZ and the SWRZ (*25*, *26*).

We also estimate how the 2002 to 2005 intrusion has influenced the flank stability and affected the potential for slumping of the flanks and for decollement earthquakes under the flanks of the volcano. We evaluate changes of the Coulomb failure stress (*27*, *28*) resolved for seaward motion along nearly horizontal faults in a cross section roughly perpendicular to the rift zone. An increase of the Coulomb failure stress encourages faulting, and a decrease discourages faulting, respectively. In the central section of the volcanic edifice, the changes in Coulomb failure stress are negative above sea level but positive below sea level (Fig. 4). The strongest stress changes occur at about 5- to 7-km depth under the southeast flank because of the combined effect of rift intrusion and chamber inflation. In the shallow southeast flank, the stress changes are also positive. The 2002 to 2005 intrusion stabilized the summit section of the volcanic edifice, discouraging landslide-type motion, but strongly destabilized the deep part of the edifice, making it prone to earthquakes along horizontal faults such as the decollement. Changes in Coulomb failure stress are 0.1 MPa and larger in most places of the seismogenic decollement fault. Bearing in mind that stress changes as low as 0.01 MPa can trigger earthquakes (*28*), the below–sea level portion of Mauna Loa has clearly been destabilized by the magma intrusion. Faulting along the decollement fault would be consistent with the previously observed pattern of alternating rift intrusions and decollement earthquakes (*22*). Indeed, aseismic motion along subhorizontal faults may already have been occurring during 2002 to 2005, but it is difficult to constrain with surface measurements.

Our analysis leads to a new model for Mauna Loa's magmatic system. During 2002 to 2005, most of the magma generated in the mantle, possibly at the depth of the subcrustal seismicity, rose into the deep and intermediate section of the rift zone, whereas only a small percentage rose into the shallow magma chamber. Intrusion of the magma changes the stress field within the volcanic edifice and encourages dike propagation into the shallow SWRZ and faulting along subhorizontal faults in most parts of the volcanic edifice, including along the decollement fault. Mauna Loa volcano likely exhibits a cyclic behavior such that deformation due to earthquakes and intrusions encourages new intrusions elsewhere in the rift zone and fault slip under the flanks.

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14. The volume-change rates are $\Delta V_{McTigue} = 0.2 \times 10^6$ m^3/year and $\Delta V_{dike} = 21.6 \times 10^6$ m^3/year. For the model coordinates, see fig. S1. The pseudo-95% confidence intervals for the depth, radius, and excess-pressure rate range from 3.5 to 7 km, 0.8 to 1.3 km, and 1.2 to 3.1 MPa/year, respectively (fig. S2). Only 1% of the magma accumulation occurs in the shallow reservoir, but its location and volume-change rate are relatively well constrained because the data resolve shallow sources well. The difference in the inferred volume-change rate for the magma chamber compared with that of the previous model occurs because of different treatment of the dike-like magma body.
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Supporting Online Material
www.sciencemag.org/cgi/content/full/316/5827/1026/DC1
Material and Methods
Table S1
Figs. S1 to S4
References

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FT Protein Movement Contributes to Long-Distance Signaling in Floral Induction of *Arabidopsis*

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In plants, seasonal changes in day length are perceived in leaves, which initiate long-distance signaling that induces flowering at the shoot apex. The identity of the long-distance signal has yet to be determined. In *Arabidopsis*, activation of *FLOWERING LOCUS T* (*FT*) transcription in leaf vascular tissue (phloem) induces flowering. We found that *FT* messenger RNA is required only transiently in the leaf. In addition, FT fusion proteins expressed specifically in phloem cells move to the apex and move long distances between grafted plants. Finally, we provide evidence that FT does not activate an intermediate messenger in leaves. We conclude that FT protein acts as a long-distance signal that induces *Arabidopsis* flowering.

Perception of day length takes place in the leaf, whereas flowers are formed by the shoot apical meristem at the apex of the shoot (*1*, *2*). A long-distance signal, called florigen or the floral stimulus, has been demonstrated to be transmitted through the phloem vascular system from the leaves to the meristem, although the identity of this signal has remained unclear since the 1930s. Molecular-genetic approaches in *Arabidopsis* have defined a regulatory pathway that promotes flowering in response to long days (LDs) and have suggested how this pathway responds to day length (*3*–*5*). Under LDs, the CONSTANS (CO) transcriptional regulator activates transcription of *FLOWERING LOCUS T* (*FT*) in the vascular tissue of leaves (*6*–*8*). *FT* encodes a small protein with similarity to RAF-kinase inhibitors that acts at the meristem together with the transcription factor FD to activate transcription of the floral meristem identity gene *APETALA1* (*7*, *9*–*11*). *FT* is expressed in the leaves in response to photoperiod, but FT protein

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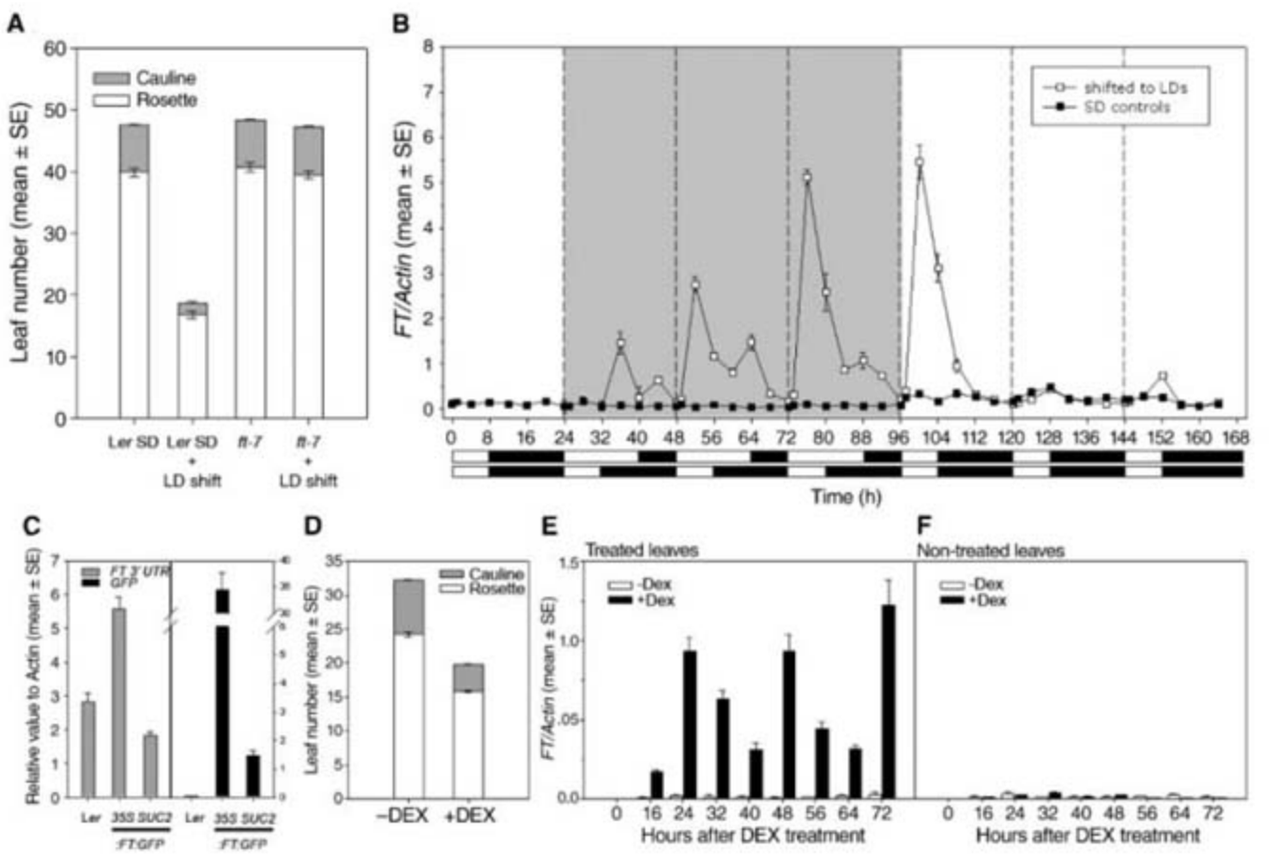

Fig. 1. Regulation of *FT* mRNA in leaves during flowering. (**A**) Flowering time of wild-type *Ler* and *ft-7* plants grown for 2 weeks under SD and exposed to three inductive LDs before return to SDs. (**B**) Expression of *FT* mRNA during 7 days comprising one SD followed by three LDs and then three subsequent SDs. *FT* mRNA expression in the SD-grown controls is also shown. RNA was tested every 4 hours. The inserted three LDs are shaded. Below the graph, bars show the duration of day (white) and night (black) for the shift experiment (top) and the control experiment (bottom). (**C**) Endogenous *FT* mRNA [FT 3′ untranslated region (UTR)] and *FT:GFP* mRNA (GFP) expression in 14-day-old *Ler*, *35S:FT:GFP*, and *SUC2:FT:GFP* plants. (**D**) Leaf number at flowering of *CO:CO:GR*, *co-2* plants treated (+DEX) or not treated (–DEX) with dexamethasone. Plants were grown for 2 weeks in SD conditions and then shifted to LDs for 4 days. Dexamethasone was applied during the LD treatment. (**E** and **F**) *FT* mRNA expression in treated (E) and nontreated (F) leaves of *CO:CO:GR* plants.

acts in the meristem to promote gene expression, suggesting that a product of *FT* may be transported to the meristem as the floral stimulus (*6*, *7*, *9*). Experiments indicating that *FT* mRNA comprises the transmissible signal have recently been retracted (*12*). Furthermore, the floral stimulus, but no detectable mRNA of genes similar to *FT*, crossed the junction between grafted tomato plants (*13*). We examined the requirement for *FT* expression in the leaves during floral induction and explored the possibility that FT protein comprises the floral stimulus.

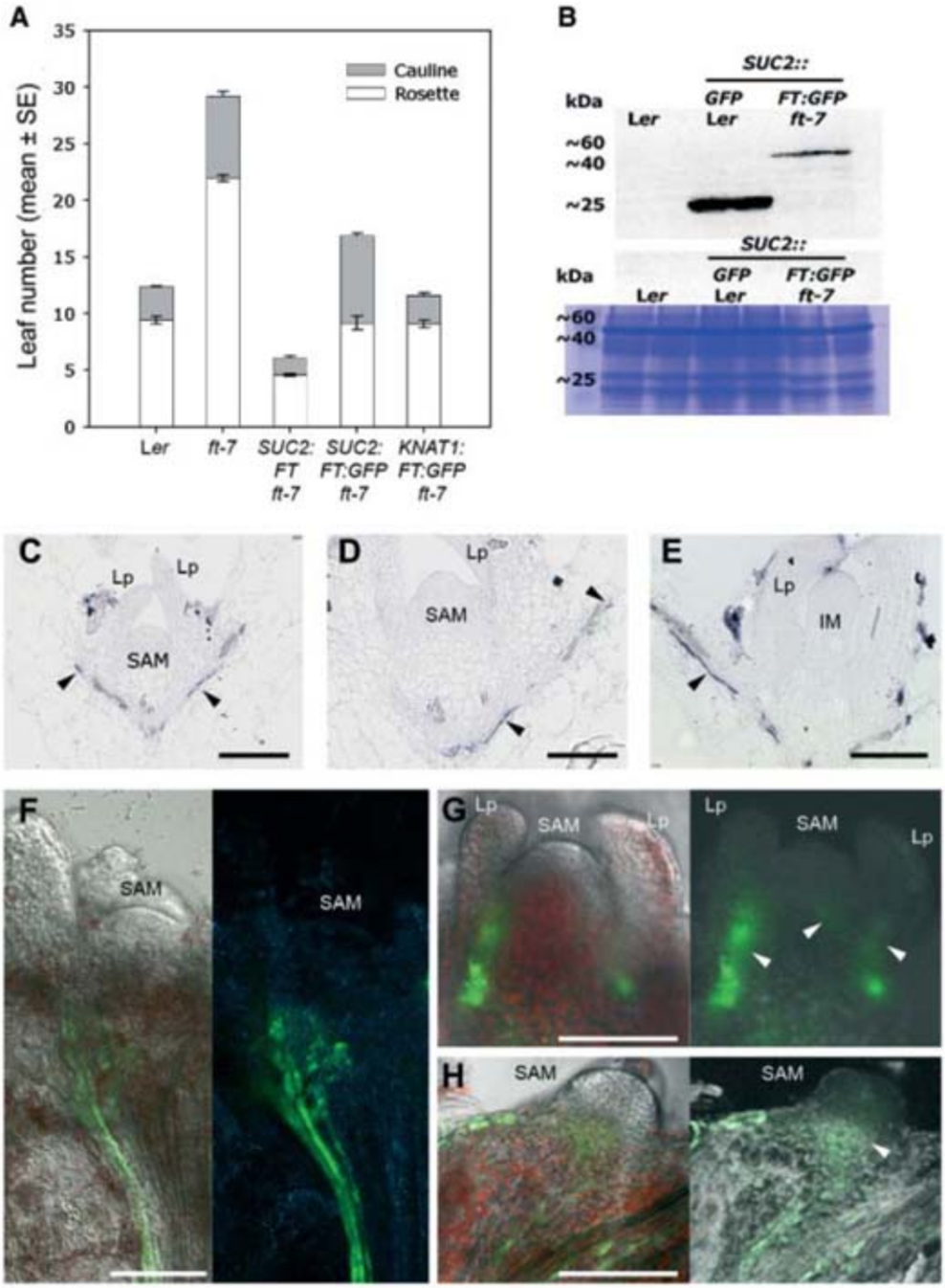

Fig. 2. Analysis of FT:GFP protein distribution in *SUC2:FT:GFP ft-7*. (**A**) Flowering time expressed as total leaf number (rosette and cauline) of representative transformants grown in LDs and compared with *Ler* and *ft-7*. (**B**) Western blot analysis showing expression of the intact FT:GFP fusion protein in *SUC2:FT:GFP ft-7* plants. *SUC2:GFP Ler* and *Ler* were used as positive and negative controls, respectively. The Comassie-stained gel acts as loading control. (**C** and **D**) In situ hybridization of apices of *SUC2:FT:GFP ft-7* plants grown for 8 extended short days (ESDs) (C) and 10 ESDs (D) and probed with a chimeric RNA fragment spanning the junction between *FT* and *GFP* in *FT:GFP*. The hybridization signal is restricted to the mature phloem (arrowheads). (**E**) In situ hybridization of a 12-ESD-old *SUC2:CO co-2* apex probed with *FT*. (**F** to **H**) Confocal analysis of the distribution of the GFP fluorescence produced by the FT:GFP fusion protein in the apical region of *SUC2:FT:GFP ft-7* transgenic plants. Images on the right show GFP signals separated from background emissions. (F) Six-day-old vegetative plant and [(G) and (H)] 10-day-old plant that is induced to flower [fluorescence is detected in the provascular tissue and at the base of the shoot apical meristem (SAM); arrowhead]. In (H), a leaf primordium flanking the SAM was removed to facilitate visualization. Lp, leaf primordium; IM, inflorescence meristem. Scale bars, 50 μm in (C) to (E), (G), and (H); 25 μm in (F).

First, we tested whether stable induction of *FT* expression in the leaves of *Arabidopsis* is required for flowering. *Perilla* leaves exposed to appropriate photoperiods produce the floral stimulus permanently (*14*, *15*). Short day (SD)–grown *Arabidopsis* plants exposed to three LDs and then returned to SDs flowered much earlier than plants exposed only to SDs (*16*) [Fig. 1A and supporting online material (SOM) text]. *FT* expression rises during the first LD after a shift from SDs (*17*). We tested whether this increase is stable by analyzing expression of *CO* and *FT* mRNA every 4 hours for 7 days, covering the shift from SDs to LDs and back to SDs (Fig. 1B and fig. S1A). In control plants grown only in SDs, *FT* mRNA abundance remained low (Fig. 1B). In contrast, in plants exposed to three LDs, *FT* mRNA abundance was increased in each of the three LDs. However, after return to SDs, *FT* mRNA levels fell after 1 day to the low level characteristic of SD-grown plants (Fig. 1B). Therefore, in these conditions, *FT* mRNA expression is not stably maintained after exposure to LDs. However, expression of endogenous *FT* mRNA was increased in the leaves of plants in which *FT* was substantially overexpressed from a transgene (Fig. 1C). We concluded that *FT* mRNA expression at wild-type levels in the leaves for 3 days is sufficient to stably induce flowering at the shoot apical meristem and that under these conditions *FT* expression in the leaves is not maintained.

In some plants, leaves that have not been exposed to inductive day lengths can be indirectly induced to form the floral stimulus. For example, grafting a plant exposed to inductive day lengths to a second noninduced plant can cause the second plant to produce the floral stimulus (*2*, *14*). To test whether *FT* expression is induced indirectly in leaves of *Arabidopsis*, we constructed a fusion of the *CO* promoter to a gene encoding a translational fusion between CO and the rat glucocorticoid receptor binding domain (*CO:CO:GR*), and we introduced this into the *co-2* mutant. In these plants, CO activity is induced by addition of the steroid dexamethasone (dex) only under LDs, during which the *CO* mRNA accumulates in the light (*18*–*20*). Application of dex to a single leaf induced flowering and increased the amount of *FT* mRNA in the leaves to which dex was added (Fig. 1, D to F, and fig. S1C). However, no difference in *FT* mRNA abundance was detected between the untreated leaves of plants treated with dex and similar leaves from untreated plants (Fig. 1F). Therefore, no detectable indirect activation of *FT* mRNA expression occurs in *Arabidopsis* leaves under the inductive conditions used in this experiment, and activation of *FT* in a single leaf is sufficient to induce flowering.

Next, we compared the spatial distribution of *FT* mRNA and protein, exploiting transgenic plants expressing FT and FT fusion proteins from heterologous promoters exclusively in the phloem companion cells, where *CO* and *FT* are expressed in wild-type plants (*6*, *21*). The use of well-characterized

heterologous promoters prevented difficulties associated with the low abundance of *FT* mRNA in the vascular tissue of wild-type plants (*6*, *10*, *11*). The promoter of the *SUCROSE TRANSPORTER 2* (*SUC2*) gene of *Arabidopsis* is active specifically in the phloem companion cells (*22*), whereas the promoter of the *KNAT1* gene is active in the shoot apical meristem, and expression of *FT* from these promoters causes early flowering of *co-2* mutants (*6*). A gene fusion comprising *FT* and *GREEN FLUORESCENT PROTEIN* (*GFP*) was constructed and expressed from the *SUC2*, *FT*, and *KNAT1* promoters. Introduction of *SUC2:FT:GFP*, *KNAT1:FT:GFP*, and *FT:FT:GFP* into *ft-7* mutants caused these plants to flower much earlier than *ft-7*, although slightly later than *SUC2:FT ft-7* or *FT:FT ft-7* (Fig. 2A and fig. S2). Protein was extracted from seedlings of *SUC2:FT:GFP* and *SUC2:GFP* plants and probed with a GFP antibody. The fusion protein was present in *SUC2:FT:GFP* plants, and importantly no free GFP protein was detected (Fig. 2B). Taken together, these results indicate that FT:GFP promotes flowering, although it is slightly less active than the wild-type FT protein.

The spatial distribution of FT:GFP protein and mRNA were then compared in *SUC2:FT:GFP* plants. *FT:GFP* and *FT* mRNAs were strongly detected in the mature phloem tissue where the *SUC2* promoter is active, but no mRNA was detected in the shoot apical meristem or protophloem (Fig. 2, C to E). The distribution of FT:GFP protein was then tested by confocal microscopy. In 6-day-old plants, which had not undergone the transition to flowering, FT:GFP was detected in the vascular tissue of the shoot (Fig. 2F). In 10-day-old plants, which were about to undergo the floral transition and had not yet formed floral primordia, FT:GFP was also detected in the provasculature at the shoot apex and at the base of the shoot apical meristem (Fig. 2, G and H). FT:GFP was detected in provasculature and apical tissues in which FT:GFP mRNA was not detected (compare Fig. 2, D and G). These results suggest that FT:GFP protein moves from the phloem companion cells to the meristem (SOM text). Such movement could occur through symplastic unloading from the phloem into the apical meristem region (*23*).

To test for movement of FT:GFP protein over longer distances, transgenic *SUC2:FT:GFP ft-7* plants were grafted to *ft-7* mutants. Sugars and other contents of the phloem sieve elements are transported from mature leaves down to the root and upward to the shoot apex. First, the aerial parts of *SUC2:FT:GFP* seedlings were grafted to *ft-7* roots. After grafting, FT:GFP protein was detected across the graft junction and in the vasculature of the *ft-7* root stock, which represents a strong sink for contents of the phloem (Fig. 3, A and B). No *FT:GFP* mRNA could be detected in these root stocks by reverse transcription polymerase chain reaction after 40 cycles of amplification (Fig. 3C). A *SUC2:FT:GFP* shoot was then grafted as a donor to

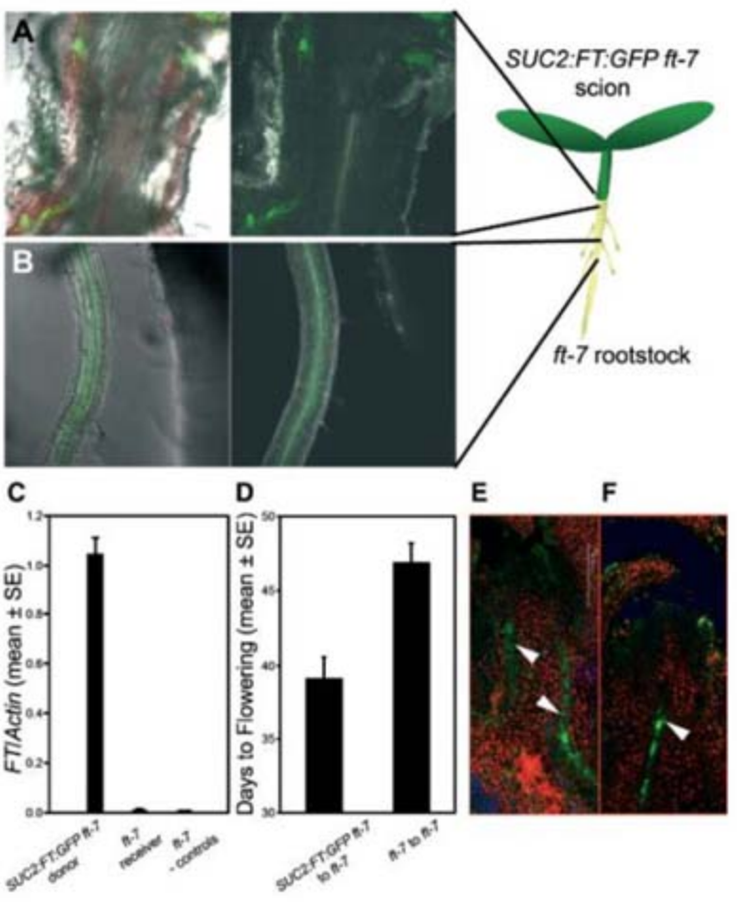

Fig. 3. Grafting of *SUC2:FT:GFP ft-7* plants to *ft-7* mutants. (**A** to **C**) Root grafting: Distribution of the FT:GFP fusion protein and *FT:GFP* mRNA. Confocal analysis of the distribution of FT:GFP fusion protein demonstrates that the protein is able to cross a graft junction (A) and can be detected in the vascular bundles of the *ft-7* root stock (B). The images on the right in (A) and (B) show GFP signals separated from background emissions. (C) *FT* cDNA amplification from the roots of *SUC2:FT:GFP ft-7* donor plants, *ft-7* root stock (labeled receiver) and *ft-7* controls. No difference was detected between the *ft-7* root stocks and *ft-7* controls. (**D**) Flowering time of *ft-7* mutants grafted to *SUC2:FT:GFP* or to *ft-7* donors. (**E** and **F**) Shoot grafting: Distribution of the FT:GFP fusion protein in the apical region of the *SUC2:FT:GFP ft-7* donor (E) and grafted *ft-7* receiver (F). The fusion protein can be detected in the vasculature of the donor and receiver (arrowheads).

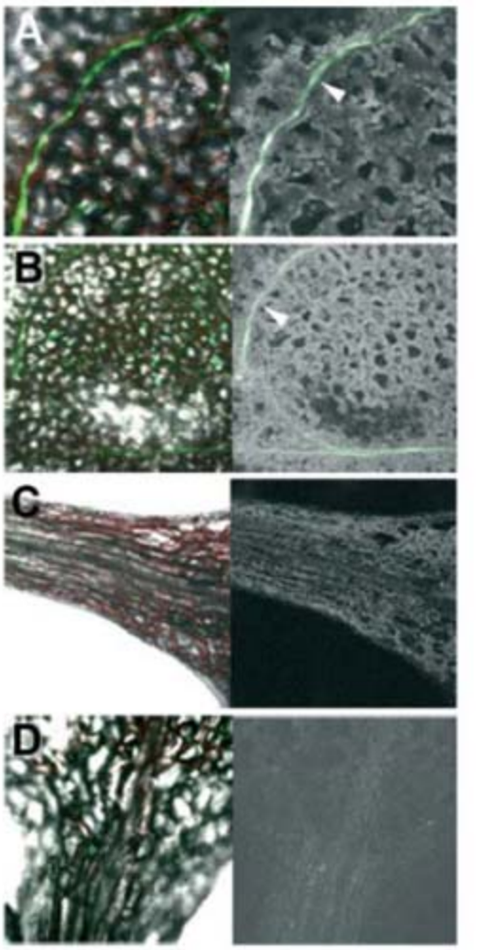

Fig. 4. Expression of FT:GFP in the minor veins alters gene expression patterns but does not induce flowering. (**A** to **D**) Confocal images of leaves expressing *GAS1:FT:GFP:GFP ft-7*. The GFP signal is detected in the minor veins [arrows in (A) and (B)] but not in the petiole (C) or the midrib (D). (**E**) Flowering time of *GAS1:FT ft-7* and *GAS1:FT:GFP ft-7* as compared with *Ler* and *ft-7* grown in LDs. (**F**) *FUL* expression in leaves of the same plants.

an *ft-7* shoot receiver. These receiver shoots flowered slightly earlier than receiver shoots on control grafts (Fig. 3D and fig. S3), as observed previously for grafts of wild-type plants to *ft-7* mutants (*24*), and FT:GFP protein was clearly detected in the vascular tissue of the shoot receiver (Fig. 3, E and F). The grafting experiments support long-distance movement of FT:GFP protein in the phloem.

Two general models could explain the role of FT in floral induction. The first proposes that a product of *FT* expressed in the leaves moves to the meristem and initiates flowering through the activation of flowering-time genes such as *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1* (*SOC1*) (*7*, *25*, *26*). Our data support movement of the protein. The second model suggests that *FT* expression in the leaves activates a second messenger, which is transmitted to the apex and induces flowering, perhaps through activation of *FT* genes or genes similar to *FT* in the meristem. We refer to this second model as a relay model: FT protein could move along with a second messenger but not comprise a signal.

We used transgenic plants expressing FT and FT:GFP from additional phloem promoters to test the relay model. The *GALACTINOL SYNTHASE* (*GAS1*) promoter is active specifically in the phloem companion cells of the minor veins of leaves (*27*) and not in the companion cells of the shoot or major veins of the leaf. *GAS1:CO* promotes early flowering of *co-1* mutants (*28*). We constructed *GAS1:FT*, *GAS1:FT:GFP*, and *GAS1:FT:GFP:GFP* transgenes and introduced these into *ft-7* mutants. In plants expressing the fusion proteins, GFP was detected only in the minor veins of the leaves (Fig. 4, A to D). *GAS1:FT* complemented the *ft-7* mutation, and the transgenic plants flowered earlier than did wild-type plants (Fig. 4E). However, *GAS1:FT:GFP ft-7* plants were as late flowering as *ft-7* mutants (Fig. 4E). Nevertheless, FT:GFP is biochemically active in the leaves of *GAS1:FT:GFP* plants. Expression of *FRUITFULL* (*FUL*) mRNA is increased in the leaves of transgenic *Arabidopsis* plants that express high levels of *FT* mRNA (*29*). *FUL* mRNA levels were higher in *GAS1:FT ft-7* and *GAS1:FT:GFP ft-7* than in wild-type plants and *ft-7* mutants (Fig. 4F). Thus FT:GFP is active in the leaves of *GAS1:FT:GFP* plants, but in contrast to *GAS1:FT* or *SUC2:FT:GFP*, this construct does not promote flowering. The larger FT:GFP protein may move less effectively to the meristem from the minor veins than from the larger veins in which *SUC2* is also active, or downloading from the companion cells to the minor veins may be differentially regulated compared with downloading to major veins. Thus, FT:GFP activity in the leaves of *GAS1:FT:GFP* plants was not sufficient to promote flowering, arguing for direct movement of an *FT* product to the meristem.

We conclude (i) that during floral induction of *Arabidopsis*, transient expression of *FT* in a single leaf is sufficient to induce flowering and (ii) that in response to *FT* expression, a signal moves from the leaves to the meristem. This signal is unlikely to be a second messenger activated by FT in the leaves given that *GAS1:FT:GFP* is active in leaves but does not promote flowering (Fig. 4). In contrast, we propose that FT protein is transported through the phloem to the meristem. Our data provide evidence for movement of FT:GFP from the phloem companion cells of *SUC2:FT:GFP* plants to the meristem that correlates with flowering, and of FT:GFP protein across graft junctions, consistent with the detection of proteins similar to FT in the phloem of *Brassica napus* plants (*30*). The data in the Report by Tamaki *et al.* (*31*) demonstrate that this function of FT is highly conserved in rice. The presence of a wide range of different proteins in phloem sap suggests that long-distance movement of proteins is the basis of other signaling processes in plants (*23*), in addition to the shorter-distance movement of proteins between neighboring cells (*32*) and previous indications of the importance of long-distance mRNA movement (*33*, *34*).

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Hd3a Protein Is a Mobile Flowering Signal in Rice

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Florigen, the mobile signal that moves from an induced leaf to the shoot apex and causes flowering, has eluded identification since it was first proposed 70 years ago. Understanding the nature of the mobile flowering signal would provide a key insight into the molecular mechanism of floral induction. Recent studies suggest that the *Arabidopsis FLOWERING LOCUS T* (*FT*) gene is a candidate for encoding florigen. We show that the protein encoded by *Hd3a*, a rice ortholog of *FT*, moves from the leaf to the shoot apical meristem and induces flowering in rice. These results suggest that the Hd3a protein may be the rice florigen.

The flowering time of plants is determined by a number of environmental factors (*1*–*3*), among which day length (photoperiod) is a major factor (*4*). On the basis of the day length, which promotes flowering, plants are grouped into two major classes: long-day (LD) and short-day (SD) plants. *Arabidopsis* is a LD plant and rice is a SD plant. *FT* is a major floral activator (*5*, *6*), which is expressed in the vascular tissue of leaves (*7*, *8*). FT protein interacts with a transcription factor FD, which is expressed only in the shoot apical meristem (SAM) (*9*, *10*). The difference in expression site implies that FT protein must move to the SAM to interact with FD for flower induction. Therefore, *FT* is a primary candidate for encoding florigen (*11*), a mobile flowering signal.

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A tomato ortholog of *FT*, *SFT*, induced early flowering, and grafting *sft* mutant shoots to *35S::SFT* donors induced normal flowering in the *sft* shoots (*12*). However, *SFT* mRNA was not detected in the SAM of the grafted tomato plants (*12*), suggesting that *SFT* mRNA does not move through graft junctions in tomato. Furthermore, a previous study suggesting that florigen was an RNA molecule has been retracted (*13*). Therefore, although *FT* is a candidate for encoding florigen, the exact nature of florigen remains to be determined.

Previous studies indicate that *Hd3a* is the major activator of flowering in rice, a SD plant, under SD conditions, and that *Hd3a* complements *Arabidopsis ft* mutants (*14*–*17*). Therefore, we examined *Hd3a* transcript levels in several tissues by real-time polymerase chain reaction (PCR) under inductive conditions for flowering (Fig. 1A). *Hd3a* mRNA accumulates in leaf blade tissue, but is present at very low abundance in leaf sheath (Fig. 1A). Quantitative comparisons of *Hd3a* mRNA in leaves and the shoot apex indicate that its accumulation in the shoot apex is on the order of 10^{-4} of that in leaf blade, indicating that *Hd3a* mRNA is virtually absent from the shoot apex of rice plants when flowering is induced under SD conditions. Therefore, it is unlikely that *Hd3a* mRNA moves from leaf to the SAM in any appreciable amount.

A *Hd3a* mRNA expression (*Hd3a* /*Ubq*)

	shoot apex	root	stem	leaf sheath	leaf blade
Exp.1	0.000110	0.001198	0.000572	0.020595	1.847840
Exp.2	0.000032	0.000464	0.000392	0.022141	1.530193

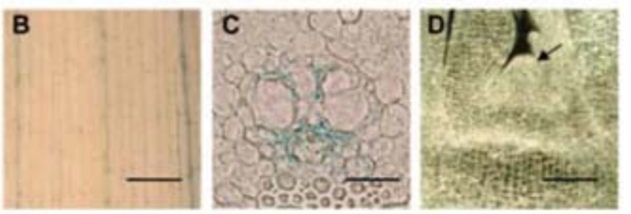

Fig. 1. Expression of *Hd3a* mRNA in rice under SD conditions. (**A**) Real-time quantitative RT-PCR of *Hd3a* mRNA accumulation in rice tissue. Samples of plants were harvested at ZT 0 to 4. *Hd3a* mRNA was quantified relative to *Ubiquitin* (*Ubq*) mRNA. (**B** to **D**) GUS staining of *Hd3a::GUS*. (B) Leaf blade of the *Hd3a::GUS* transgenic rice plant at ZT4 on day 35 under SD conditions. (C) Transverse section of a leaf blade in (B). (D) Longitudinal section of the SAM (arrow) of the same transgenic plant as in (B) and (C). Scale bars: 1 mm (B), 20 μm (C), 50 μm (D).

To determine the tissue and cell specificity of *Hd3a* mRNA expression, we analyzed the activity of an *Hd3a::GUS* transgene in leaf blades and SAMs of transgenic rice. The promoter activity of *Hd3a* was detected in phloem and xylem parenchyma cells of leaf blade (Fig. 1, B and C), and no GUS activity was detected in the SAM (Fig. 1D). This was consistent with the quantitative reverse transcription–polymerase chain reaction (RT-PCR) results (Fig. 1A) and similar to the tissue specificity of *FT* expression in *Arabidopsis* (*7*, *18*). *Hd3a* expression is thus restricted to the vascular tissues of rice leaves under inductive SD conditions.

To study the function and localization of Hd3a protein in rice, we fused the 1.7-kb *Hd3a* promoter used for GUS analysis to green fluorescent protein and introduced the resulting construct (*Hd3a:GFP*) into rice plants by *Agrobacterium*-mediated transformation. The leaf diurnal expression pattern of transgenic plants was similar to that of the endogenous *Hd3a* gene (Fig. 2L), but varied among transgenic plants. Transgenic rice plants flowered (headed) significantly earlier than wild-type plants (Table 1 and fig. S1A), suggesting that expression of *Hd3a:GFP* causes early flowering, because expression of endogenous *Hd3a* mRNA in transgenic rice plants did not change relative to that in wild-type plants.

To examine tissue localization of the Hd3a protein in *Hd3a:GFP* transgenic plants, we analyzed GFP fluorescence in the SAM, the upper part of the stem, and in the leaf blade by confocal laser scanning microscopy. GFP fluorescence was limited to the inner conelike region of the SAM in transgenic rice (Fig. 2, A to D, G and H). The GFP signal was detected in the SAM (Fig. 2, C and D) and stem vascular tissue (Fig. 2, I and J). GFP signal was also detected in the vascular tissue of the upper part of the stem and in the region just beneath the meristem where nodes are present (Fig. 2, E and F), suggesting that Hd3a:GFP protein moves from the end of the vascular bundles through the basal cells and into the SAM.

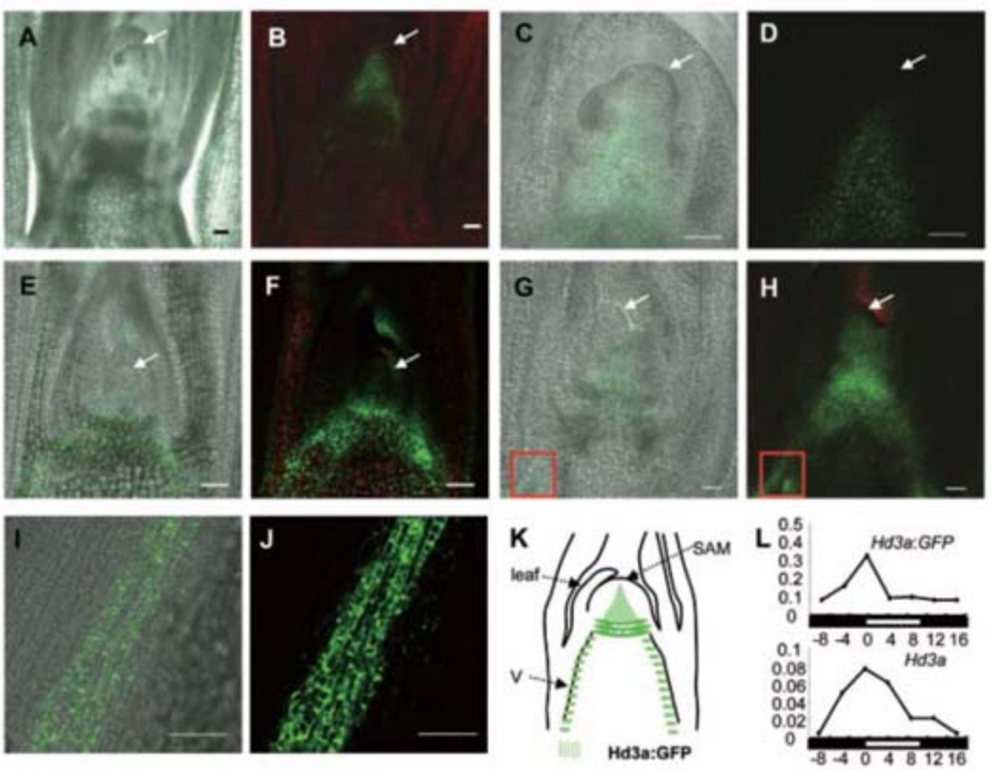

Fig. 2. Confocal microscopy of *Hd3a::Hd3a-GFP* transgenic rice. (**A** to **J**) Confocal images of *Hd3a::Hd3a-GFP* transgenic plants. (A to H) Longitudinal sections through the SAM. (I and J) Longitudinal section through vascular bundles indicated by the red squares in (G) and (H). (A), (C), (E), (G), and (I) are composite images of the fluorescein isothiocyanate (FITC) and transmission channels. (B), (D), (F), (H), and (J) show the spectrally unmixed images. Hd3a-GFP fluorescence is shown in green, and plant autofluorescence in red. Scale bars, 50 μm. Arrows indicate a SAM. (**K**) Diagram of the SAM and the upper part of the rice stem. V, vascular bundles; SAM, shoot apical meristem. (**L**) Real-time quantitative RT-PCR of *Hd3a-GFP* and endogenous *Hd3a* mRNAs under SD conditions in *Hd3a::Hd3a-GFP* transgenic rice plants. White and black bars at the bottom represent light and dark periods, respectively.

Table 1. Flowering (Heading) times of transgenic plants under SD conditions.

Genotype	Days to flowering (days ± SE)	*n*
Wild type	50.4 ± 7.6	5
Hd3a::Hd3a:GFP	32.8 ± 11.2	6
RPP16::Hd3a:GFP	14.8 ± 3.3	5
RPP16::GFP	64	2
rolC::Hd3a:GFP*	19.5 ± 13.6	11
rolC::GFP*	88.6 ± 11.3	5

*Indicates significant difference from control by Student's *t* test ($P = 0.0000007$).

Hd3a:GFP protein is thus found in the inner region of the SAM and in stem and leaf blade vascular tissues, suggesting that it is produced in the vascular tissue of the leaf blade, transported through stem phloem tissue, unloaded at the upper end of the vascular tissue, and translocated to the SAM, probably through the region just beneath the SAM. These results suggest that the Hd3a protein, but not *Hd3a* mRNA, is a candidate for the florigen in rice.

We expressed the *Hd3a:GFP* gene in phloem tissue by fusing it with two phloem-specific promoters, the *Agrobacterium rhizogenes rolC* promoter (*8*, *18*) and *Rice Phloem Protein 16* (*RPP16*) promoter (*19*). The *rolC* promoter is specifically active in the phloem (*18*), and *rolC::CO* is known to induce extremely early flowering in *Arabidopsis* (*8*). The *RPP16* gene encodes a phloem-specific protein in rice (*19*). Rice plants expressing *RPP16::Hd3a:GFP* and *rolC::Hd3a:GFP* flowered very early compared to the wild-type plant (Table 1 and fig. S1, B and C), indicating that the vascular-specific expression of the *Hd3a:GFP* gene induced early flowering in rice. GFP signals were detected in the vascular tissues of leaf blades and in the stems of *rolC::Hd3a:GFP* and *RPP16::Hd3a:GFP* transgenic plants (Fig. 3, B, D, J, and L). In transverse sections of the leaf blade, GFP signals were detected in cells near the phloem (Fig. 3, A, B, I, and J). The intact Hd3a:GFP protein was detected by immunoblotting with antibody to GFP in the leaf extract (fig. S2). Fluorescence was detected in the SAMs of both transgenic lines (Fig. 3, E, F, M, and N), and in leaves adjacent to SAMs (Fig. 3, E, F, M, and N). Because the free GFP protein diffused in many tissues in rice, the Kaede reporter protein (*20*, *21*) was used to localize promoter activity. The Kaede protein forms a monotetrameric complex of 116 kD and is retained in cytoplasm (*20*). Kaede fluorescence was not detected in the SAM (Fig. 3, G, H, O, and P) and was detected only in the vascular tissues of *rolC::Kaede* and *RPP16::Kaede* transgenic plants (fig. S3), demonstrating that the *rolC* and *RPP16* promoters are not active in the SAM. This result confirms that Hd3a protein is translocated from stem vascular tissue to the SAM.

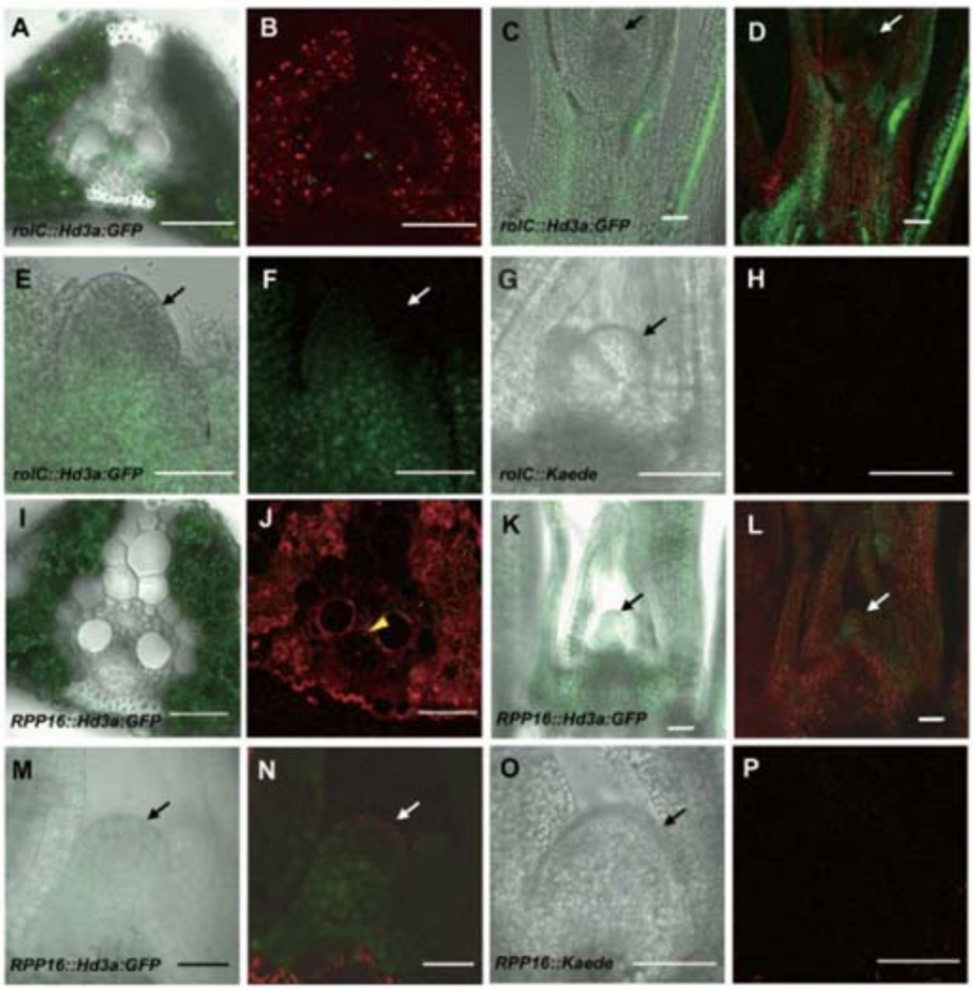

Fig. 3. Confocal microscopy of transgenic rice plants expressing a fusion of reporter protein with phloem-specific promoters. Confocal images of transgenic rice plants. (**A**), (**C**), (**E**), (**G**), (**I**), (**K**), (**M**), and (**O**) are composite images of FITC and transmission channels. (**B**), (**D**), (**F**), (**H**), (**J**), (**L**), (**N**), and (**P**) show the spectrally unmixed images. Hd3a-GFP and Kaede-green fluorescence are shown in green, and autofluorescence is in red. (A) and (B) Transverse sections through a leaf of *rolC::Hd3a-GFP*. (C) and (D) Longitudinal sections through the stem and SAM of *rolC::Hd3a-GFP*. (E) and (F) Longitudinal section through a SAM of *rolC::Hd3a-GFP*. (G) and (H) Longitudinal sections through a SAM of *rolC::Kaede*. (I) and (J) Transverse section through a leaf of *RPP16::Hd3a-GFP*. (K) and (L) Longitudinal sections through a stem, including the meristem of *RPP16::Hd3a-GFP*. (M) and (N) Longitudinal sections through a meristem of *RPP16::Hd3a-GFP*. (O) and (P) Longitudinal sections through the SAM of *RPP16::Kaede*. Scale bars: 25 μm [(A), (B), (M), and (N)]; 50 μm [(C to L), (O), and (P)]. Arrows indicate SAM. Arrowheads indicate GFP fluorescence.

Hd3a protein fulfills the requirements for a florigen (*11*), but *Hd3a* mRNA cannot be completely ruled out as a florigen because *Hd3a* transcripts are present in the shoot apex in extremely low abundance. A recent proteomic study of phloem sap obtained from the inflorescence stem of *Brassica napus* identified FT protein (*22*) as a sap constituent. The presence of FT ortholog in the corresponding tissues of this distantly related plant supports our conclusion that it is the Hd3a protein that acts as the main florigen. Our results strongly suggest that the protein encoded by *FT/Hd3a* acts universally as a florigen (*23*–*25*).

Because there is no vascular connection between the upper end of the vascular bundles and the base of the SAM, there must be some mechanisms that regulate the movement of Hd3a protein into the SAM. There may be intercellular transport proteins which help Hd3a protein move toward the center of the stem just beneath the SAM. Once Hd3a protein enters the SAM, it may be localized in the nucleus. A recent report on the maize *FD* ortholog (*26*) shows that its mRNA is localized in the inner region of the SAM, similar to the region where GFP signal was detected in *Hd3a:GFP* transgenic rice. These results suggest that an FD-like nuclear protein may regulate intracellular localization of Hd3a protein in the SAM.

The morphology of vegetative organs changes when there is a phase transition to flowering in some species. It has recently been shown that *FT* overexpression induces changes in leaf morphology and stem branching in tomato (*12*) and in *Arabidopsis* leaf morphology (*27*). In aspen trees, *FT* was shown to regulate growth cessation and bud dormancy (*28*). We found that transgenic rice plants expressing *RPP16::Hd3a:GFP* or *rolC::Hd3a:GFP* had alterations in multiple traits in vegetative organs such as elongation of internodes, which is known to occur after the transition to flowering and increased tillering. These alterations were induced by ectopic expression of the Hd3a protein in the vascular tissues. These results may suggest that many, if not all, of the changes associated with the transition from vegetative to reproductive growth and development induced by day length are induced by Hd3a protein. Therefore, Hd3a/FT protein may be a general mobile morphogen that regulates multiple phases of plant growth by photoperiod.

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The Increasing Dominance of Teams in Production of Knowledge

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We have used 19.9 million papers over 5 decades and 2.1 million patents to demonstrate that teams increasingly dominate solo authors in the production of knowledge. Research is increasingly done in teams across nearly all fields. Teams typically produce more frequently cited research than individuals do, and this advantage has been increasing over time. Teams now also produce the exceptionally high-impact research, even where that distinction was once the domain of solo authors. These results are detailed for sciences and engineering, social sciences, arts and humanities, and patents, suggesting that the process of knowledge creation has fundamentally changed.

An acclaimed tradition in the history and sociology of science emphasizes the role of the individual genius in scientific discovery (*1*, *2*). This tradition focuses on guiding contributions of solitary authors, such as Newton and Einstein, and can be seen broadly in the tendency to equate great ideas with particular names, such as the Heisenberg uncertainty principle, Euclidean geometry, Nash equilibrium, and Kantian ethics. The role of individual contributions is also celebrated through science's award-granting institutions, like the Nobel Prize Foundation (*3*).

Several studies, however, have explored an apparent shift in science from this individual-based model of scientific advance to a teamwork model. Building on classic work by Zuckerman and Merton, many authors have established a rising propensity for teamwork in samples of research fields, with some studies going back a century (*4*–*7*). For example, de Solla Price examined the change in team size in chemistry from 1910 to 1960, forecasting that in 1980 zero percent of the papers would be written by solo authors (*8*). Recently, Adams *et al.* established that over time, teamwork had increased across broader sets of fields among elite U.S. research universities (*9*). Nevertheless, the breadth and depth of this projected shift in manpower remains indefinite, particularly in fields where the size of experiments and capital investments remain small, raising the question as to whether the projected growth in teams is universal or cloistered in specialized fields.

A shift toward teams also raises new questions of whether teams produce better science. Teams may bring greater collective knowledge and effort, but they are known to experience social network and coordination losses that make them underperform individuals even in highly complex tasks (*10*–*12*), as F. Scott Fitzgerald concisely observed when he stated that "no grand idea was ever born in a conference" (*13*). From this viewpoint, a shift to teamwork may be a costly phenomenon or one that promotes low-impact science, whereas the highest-impact ideas remain the domain of great minds working alone.

We studied 19.9 million research articles in the Institute for Scientific Information (ISI) Web of Science database and an additional 2.1 million patent records. The Web of Science data covers research publications in science and engineering since 1955, social sciences since 1956, and arts and humanities since 1975. The patent data cover all U.S. registered patents since 1975 (*14*). A team was defined as having more than one listed author (publications) or inventor (patents). Following the ISI classification system, the universe of scientific publications is divided into three main branches and their constituent subfields: science and engineering (with 171 subfields), social sciences (with 54 subfields), and arts and humanities (with 27 subfields). The universe of U.S. patents was treated as a separate category (with 36 subfields). See the Supporting Online Material (SOM) text for details on these classifications.

For science and engineering, social sciences, and patents, there has been a substantial shift toward collective research. In the sciences, team size has grown steadily each year and nearly

Table 1. Patterns by subfield. For the three broad ISI categories and for patents, we counted the number (*N*) and percentage (%) of subfields that show (i) larger team sizes in the last 5 years compared to the first 5 years and (ii) RTI measures larger than 1 in the last 5 years. We show RTI measures both with and without self-citations removed in calculating the citations received. Dash entries indicate data not applicable.

		Increasing team size		RTI > 1 (with self-citations)		RTI > 1 (no self-citations)	
	N_{fields}	N_{fields}	%	N_{fields}	%	N_{fields}	%
Science and engineering	171	170	99.4	167	97.7	159	92.4
Social sciences	54	54	100.0	54	100.0	51	94.4
Arts and humanities	27	24	88.9	23	85.2	18	66.7
Patents	36	36	100.0	32	88.9	–	–

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doubled, from 1.9 to 3.5 authors per paper, over 45 years.

Shifts toward teamwork in science and engineering have been suggested to follow from the increasing scale, complexity, and costs of big science. Surprisingly then, we find an equally strong trend toward teamwork in the social sciences, where these drivers are much less notable. Although social scientists in 1955 wrote 17.5% of their papers in teams, by 2000 they wrote 51.5% of their papers in teams, an increase similar to that in sciences and engineering. Mean team size has also grown each year. On average, today's social sciences papers are written in pairs, with a continuing, positive trend toward larger teams. Unlike the other areas of research, single authors still produce over 90% of the papers in the arts and humanities. Nevertheless, there is a positive trend toward teams in arts and humanities ($P < 0.001$). Lastly, patents also show a rising dominance of teams. Although these data are on a shorter time scale (1975–2000), there was a similar annualized increase in the propensity for teamwork. Average team size has risen from 1.7 to 2.3 inventors per patent, with the positive trend toward larger teams continuing.

The generality of the shift to teamwork is captured in Table 1. In sciences and engineering, 99.4% of the 171 subfields have seen increased teamwork. Meanwhile, 100% of the 54 subfields in the social sciences, 88.9% of the 27 subfields in the humanities, and 100% of the 36 subfields in patenting have seen increased teamwork.

Trends for individual fields are presented in table S1. In the sciences, areas like medicine, biology, and physics have seen at least a doubling in mean team size over the 45-year period. Surprisingly, even mathematics, long thought the domain of the loner scientist and least dependent of the hard sciences on lab scale and capital-intensive equipment, showed a marked increase in the fraction of work done in teams, from 19% to 57%, with mean team size rising from 1.22 to 1.84. In the social sciences, psychology, economics, and political science show enormous shifts toward teamwork, sometimes doubling or tripling the propensity for teamwork. With regard to average team size, psychology, the closest of the social sciences to a lab science, has the highest growth (75.1%), whereas political science has the lowest (16.6%). As reflected in Fig. 1A, the humanities show lower growth rates in the fraction of publications done in teams, yet a tendency toward increased teamwork is still observed. All areas of patents showed a positive change in both the fraction of papers done by teams and the team size, with only small variations across the areas of patenting, suggesting that the conditions favoring teamwork in patenting are largely similar across subfields.

Our measure of impact was the number of citations each paper and patent receives, which has been shown to correlate with research quality (*15*–*17*) and is frequently used in promotion and funding reviews (*18*). Highly cited work was defined as receiving more than the mean number of citations for a given field and year (*19*). Teams produced more highly cited work in each broad area of research and at each point in time.

To explore the relationship between teamwork and impact in more detail, we defined the relative team impact (RTI) for a given time period and field. RTI is the mean number of citations received by team-authored work divided by the mean number of citations received by solo-authored work. A RTI greater than 1 indicates that teams produce more highly cited papers than solo authors and vice versa for RTI less than 1. When RTI is equal to 1, there is no difference in citation rates for team- and solo-authored papers. In our data set, the average RTI was greater than 1 at all points in time and in all broad research areas: sciences and engineering, social sciences, humanities, and patents. In other words, there is a broad tendency for teams to produce more highly cited work than individual authors. Further, RTI is rising with time. For example, in sciences and engineering, team-authored papers received 1.7 times as many citations as solo-authored papers in 1955 but 2.1 times the citations by 2000. Similar upward trends in relative team impact appear in sciences and engineering, social science, and arts and humanities and more weakly in patents, although the trend is still upward (*20*). During the early periods, solo authors received substantially more citations on average than teams in many subfields, especially within sciences and engineering (Fig. 2E) and social sciences (Fig. 2F). By the end of the period, however, there are almost no subfields in sciences and engineering and social sciences in which solo authors typically receive more citations than teams. Table S1 details RTIs for major individual research areas, indicating that teams currently have a nearly universal impact advantage. In a minority of cases, RTIs declined with time (e.g., –34.4% in mathematics and –25.7% in education), although even here teams currently have a large advantage in citations received (e.g., 67% more average citations in mathematics and 105% in education).

The citation advantage of teams has also been increasing with time when teams of fixed size are compared with solo authors. In science and engineering, for example, papers with two authors received 1.30 times more citations than solo authors in the 1950s but 1.74 times more citations in the 1990s. In general, this pattern prevails for comparisons between teams of any fixed size versus solo authors (table S4).

A possible challenge to the validity of these observations is the presence of self-citations, given that teams have opportunities to self-cite their work more frequently than a single author. To address this, we reran the analysis with all self-citations removed from the data set (*21*). We found that removing self-citations can produce modest decreases in the RTI measure in some fields; for example, RTIs fell from 3.10 to 2.87 in medicine and 2.30 to 2.13 in biology (table S1). Thus, removing self-citations can reduce the RTI by 5 to 10%, but the relative citation advantage of teams remains essentially intact.

Because the progress of knowledge may be driven by a small number of key insights (*22*), we further test whether the most extraordinary concepts, results, and technologies are the province of solitary scientists or teams. Pooling all papers and patents within the four research areas, we calculated the frequency distribution of citations to solo-authored and team-authored work, comparing the first 5 years and last 5 years of our data. If these distributions overlap in their right-hand tails, then a solo-authored paper or patent is just as likely as a team-authored paper or patent to be extraordinarily highly cited.

Our results show that teams now dominate the top of the citation distribution in all four research domains (Fig. 3, A to D). In the early years, a solo author in science and engineering or the social sciences was more likely than a team to receive no citations, but a solo author was also more likely to garner the highest number of citations, that is, to have a paper that was singularly influential. However, by the most recent period, a team-authored paper has a higher probability of being extremely highly cited. For example, a team-authored paper in science and engineering is currently 6.3 times more likely than a solo-authored paper to receive at least 1000 citations. Lastly, in arts and humanities and in patents, individuals were never more likely than teams to produce more-influential work. These patterns also hold when self-citations are removed (fig. S5).

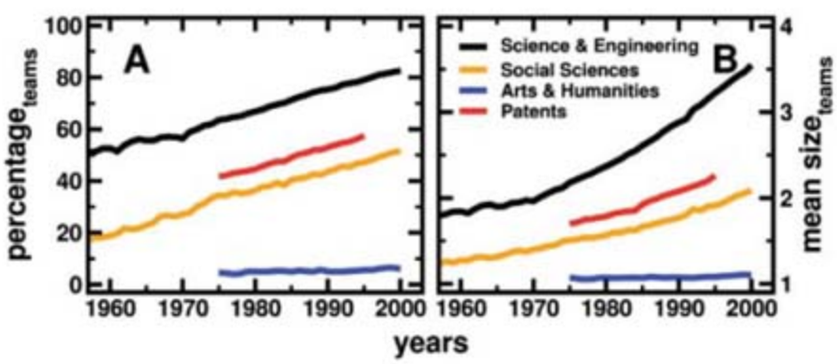

Fig. 1. The growth of teams. These plots present changes over time in the fraction of papers and patents written in teams (**A**) and in mean team size (**B**). Each line represents the arithmetic average taken over all subfields in each year.

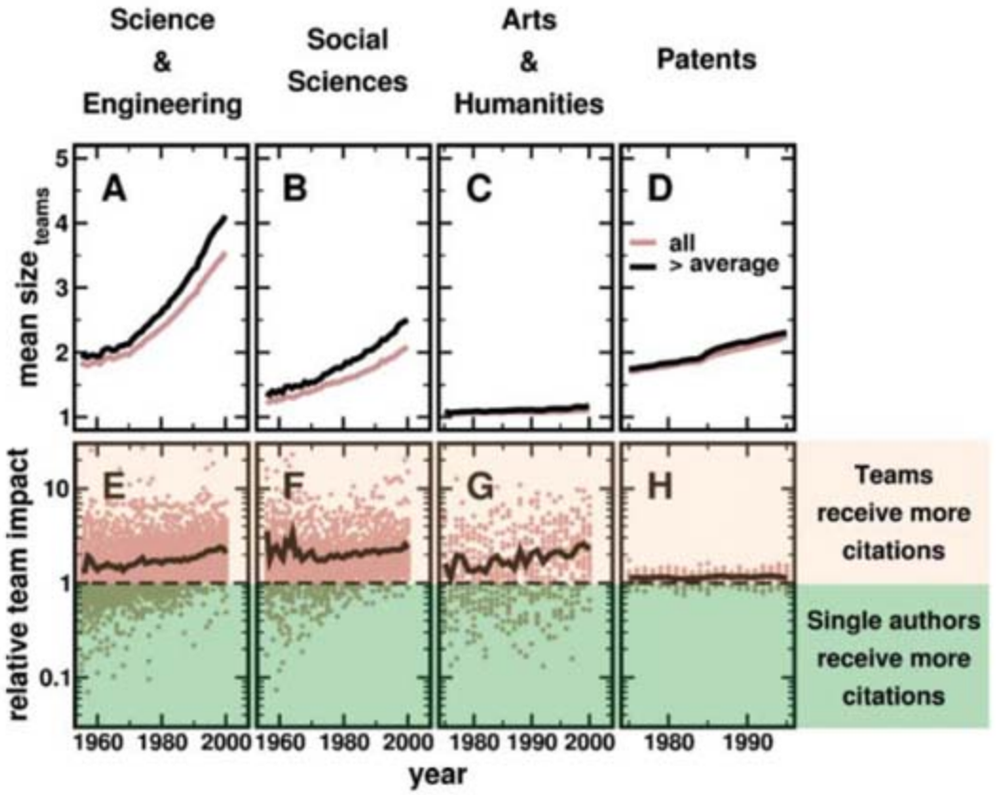

Fig. 2. The relative impact of teams. (**A** to **D**) Mean team size comparing all papers and patents with those that received more citations than average in the relevant subfield. (**E** to **H**) The RTI, which is the mean number of citations received by team-authored work divided by the mean number of citations received by solo-authored work. A ratio of 1 indicates that team- and solo-authored work have equivalent impact on average. Each point represents the RTI for a given subfield and year, whereas the black lines present the arithmetic average in a given year.

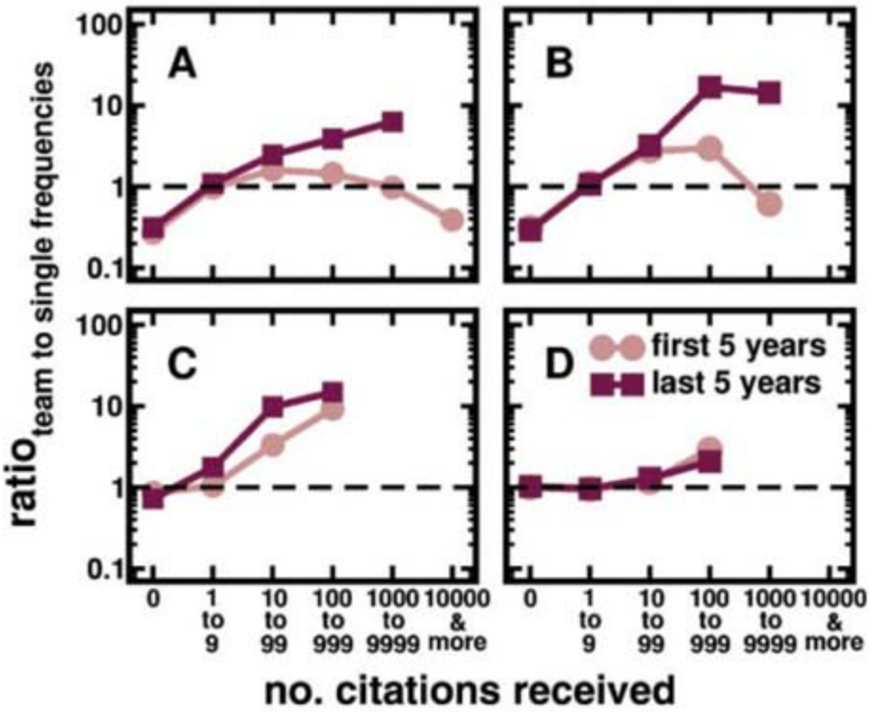

Fig. 3. Exceptional research. Pooling all publications and patents within the four research categories, we calculated frequency distributions of citations received. Separate distributions are calculated for single authors and for teams, and the ratio is plotted. A ratio greater than 1 indicates that a team-authored paper had a higher probability of producing the given range of citations than a solo-authored paper. Ratios are compared for the early period (first 5 years of available data) and late period (last 5 years of available data) for each research category, sciences and engineering (**A**), social sciences (**B**), arts and humanities (**C**), and patents (**D**).

Taken together, these results suggest two important facts about preeminent work in our observational periods. First, it never appeared to be the domain of solo authors in arts and humanities and in patents. Second, solo authors did produce the papers of singular distinction in science and engineering and social science in the 1950s, but the mantle of extraordinarily cited work has passed to teams by 2000.

Over our 5-decade sample period, the increasing capital intensity of research may have been a key force in laboratory sciences where the growth in teamwork has been intensive (*8*), but it is unlikely to explain similar patterns in mathematics, economics, and sociology, where we found that growth rates in team size have been nearly as large. Since the 1950s, the number of researchers has grown as well, which could promote finer divisions of labor and more collaboration. Similarly, steady growth in knowledge may have driven scholars toward more specialization, prompting larger and more diverse teams (*7*, *10*). However, we found that teamwork is growing nearly as fast in fields where the number of researchers has grown relatively slowly (see Supporting Online Material). Declines in communication costs could make teamwork less costly as well (*9*, *23*). Shifting authorship norms may have influenced coauthorship trends in fields with extremely large teams, such as biomedicine and high-energy physics (*24*, *25*), and yet our results hold across diverse fields in which norms for order of authorship, existence of postdoctorates, and prevalence of grant-based research differ substantially.

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19. Citations received were counted from publication year to 2006. Recent publications have smaller citation counts because they have had less time to be cited, but this effect is standardized when comparing team versus solo publications within a given year.
20. In patenting, we may observe weaker trends because (i) citing earlier work can limit a patent's scope, so that applicants may avoid citations, and (ii) patent examiners typically add the majority of citations, which makes patent citations different from paper citations (*26*, *27*).
21. A self-citation is defined as any citation where a common name exists in the authorship of both the cited and the citing papers. All citations were removed in which a citing and cited author's first initial and last name matched. This method can also eliminate citations where the authors are different people but share the same name. However, performing Monte Carlo simulations on the data, we find that such errors occur in less than 1 of every 2000 citations. Thus, any errors introduced by this method appear negligible. We did not remove self-citations from patents because citations to previous work in the patent literature are primarily assigned by the patent examiner (*27*), who independently assigns citations to earlier work based on the relevance of previous patents' content.
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28. We thank R. Guimera, S. Stern, K. Murnighan, K. Williams Phillips, and two anonymous referees for their helpful comments. The Northwestern Institute on Complex Systems provided financial support.

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SOM Text
Figs. S1 to S5
Tables S1 to S5
References

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MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling

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The epidermal growth factor receptor (EGFR) kinase inhibitors gefitinib and erlotinib are effective treatments for lung cancers with *EGFR* activating mutations, but these tumors invariably develop drug resistance. Here, we describe a gefitinib-sensitive lung cancer cell line that developed resistance to gefitinib as a result of focal amplification of the *MET* proto-oncogene. inhibition of MET signaling in these cells restored their sensitivity to gefitinib. *MET* amplification was detected in 4 of 18 (22%) lung cancer specimens that had developed resistance to gefitinib or erlotinib. We find that amplification of *MET* causes gefitinib resistance by driving ERBB3 (HER3)–dependent activation of PI3K, a pathway thought to be specific to EGFR/ERBB family receptors. Thus, we propose that *MET* amplification may promote drug resistance in other ERBB-driven cancers as well.

Tyrosine kinase inhibitors (TKIs) are an emerging class of anticancer therapies that have shown promising clinical activity. Gefitinib (Iressa) and erlotinib (Tarceva) inhibit the epidermal growth factor receptor (EGFR) kinase and are used to treat non–small cell lung cancers (NSCLCs) that have activating mutations in the *EGFR* gene (*1*–*4*). Although most *EGFR* mutant NSCLCs initially respond to EGFR inhibitors, the vast majority of these tumors ultimately become resistant to the drug treatment. In about 50% of these cases, resistance is due to the occurrence of a secondary mutation in *EGFR* (T790M) (*5*, *6*). The mechanisms that contribute to resistance in the remaining tumors are unknown.

To explore additional mechanisms of gefitinib resistance, we generated resistant clones of the gefitinib hypersensitive *EGFR* exon 19 mutant NSCLC cell line, HCC827, by exposing these cells to increasing concentrations of gefitinib for 6 months. The resultant cell line, HCC827 GR (gefitinib resistant), and six clones isolated from single cells were resistant to gefitinib in vitro ($IC_{50} > 10\ \mu M$) (Fig. 1A). Unlike in the parental HCC827 cells, phosphorylation of ERBB3 and Akt in the HCC827 GR cells was maintained in the presence of gefitinib (Fig. 1B).

We previously observed that *EGFR* mutant tumors activate phosphoinositide 3-kinase (PI3K)/Akt signaling through ERBB3 and that down-regulation of the ERBB3/PI3K/Akt signaling pathway is required for gefitinib to induce apoptosis in *EGFR* mutant cells (*7*, *8*). In addition, persistent ERBB3 phosphorylation has also been associated with gefitinib resistance in ERBB2-amplified breast cancer cells (*9*). We therefore hypothesized that gefitinib resistance in *EGFR* mutant NSCLCs might involve sustained signaling via ERBB3. After excluding the presence of a secondary resistance mutation in *EGFR* (*10*), we investigated whether aberrant activation of another receptor might be mediating the resistance. We used a phospho–receptor tyrosine kinase (phospho-RTK) array to compare the effects of gefitinib on 42 phosphorylated RTKs in HCC827 and HCC827 GR5 cells (Fig. 1C). In the parental cell line, EGFR, ERBB3, ERBB2, and MET were all phosphorylated, and this phosphorylation was either completely or markedly reduced upon gefitinib treatment. In contrast, in the resistant cells, phosphorylation of MET, ERBB3, and EGFR persisted at higher levels in the presence of gefitinib (Fig. 1C).

We next performed genome-wide copy number analyses and mRNA expression profiling of the HCC827 GR cell lines and compared them with the parental HCC827 cells (fig. S1 and table S1). The resistant but not parental cell lines showed a marked focal amplification within chromosome 7q31.1 to 7q33.3, which contains the *MET* proto-oncogene (Fig. 1D). *MET* encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor (scatter factor), and *MET* amplification has been detected in gastric and esophageal cancers (*11*, *12*). Analysis by quantitative polymerase chain reaction (PCR) confirmed that *MET* was amplified by a factor of 5 to 10 in the resistant cells (fig. S2), and sequence analysis provided no evidence of mutations in *MET*.

To determine whether increased MET signaling underlies the acquired resistance to gefitinib, we examined whether MET inhibition suppressed growth of the resistant cells. HCC827 GR cells were exposed to PHA-665752, a MET tyrosine kinase inhibitor, alone or in combination with gefitinib (*13*). Although the HCC827 GR5 cells were resistant to both gefitinib alone and PHA-665752 alone, combined treatment resulted

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in substantial growth inhibition (Fig. 2A) and induced apoptosis (fig. S3). In the resistant cells, gefitinib alone substantially reduced phosphorylation of EGFR, and it had only minimal effects on ERBB3 and Akt phosphorylation (Fig. 2B). However, gefitinib in combination with PHA-665752 fully suppressed ERBB3 and Akt phosphorylation in the resistant cells. These findings suggest that the observed resistance in HCC827 GR cells is mediated by increased MET signaling.

To investigate the mechanism by which PI3K/Akt becomes activated in the resistant cells, we immunoprecipitated the p85 regulatory subunit of PI3K and examined coprecipitating proteins. In the parental HCC827 cell line, two major phosphotyrosine proteins, ERBB3 (~240 KD) and growth-factor-receptor–bound protein 2 (Grb2)–associated binder 1 (Gab1) (~120 KD), a known PI3K adaptor protein (*14*), coprecipitated with p85 (Fig. 2C), and both interactions were disrupted by gefitinib alone. In contrast, in the resistant cells, both ERBB3 and Gab1 remained associated with p85 in the presence of gefitinib alone. However, the combination of gefitinib and PHA-665752 completely disrupted these interactions in the resistant cell lines (Fig. 2C). As shown in Fig. 2B, ERBB3 tyrosine phosphorylation was suppressed in the resistant cells only when they were in the presence of both inhibitors, which suggests that MET can trigger the activation of ERBB3 independent of EGFR kinase activity. In the course of these studies, we noted that, although PHA-665752 alone blocked Gab-1 association with p85, it had minimal effect on Akt phosphorylation (Fig. 2, B and C). This observation suggests that the association of Gab-1 with PI3K is not necessary for Akt phosphorylation in the resistant cell lines.

To determine whether a MET/ERBB3/PI3K signaling axis was mediating resistance in these cells, we used RNA interference (RNAi) technology. Down-regulation of ERBB3 by an *ERBB3*-specific short hairpin RNA (shRNA) led to substantial inhibition of Akt phosphorylation and significantly inhibited cell growth in both resistant and parental cells (Fig. 2, D and E) In addition, two shRNAs directed against two different regions of *MET* restored gefitinib sensitivity in the resistant cells (fig. S4) (*15*). Moreover, both of the *MET*-specific shRNAs down-regulated MET to the level found in the parental HCC827 cell line (see Fig. 2B) and restored the ability of gefitinib to down-regulate both ERBB3 and Akt phosphorylation in these cells (Fig. 2F). Finally, overexpression of MET in HCC827 cells was sufficient to confer gefitinib resistance (fig. S5). Together, these findings suggest that *MET* amplification leads to persistent activation of PI3K/Akt signaling in the presence of gefitinib by maintaining ERBB3 phosphorylation.

Notably, gastric cancer cell lines with *MET* amplification exhibit an increased sensitivity to PHA-665752 (*11*). Therefore, we investigated whether other cell lines with *MET* amplification might also activate PI3K/Akt signaling through ERBB3. Interestingly, we readily detected ERBB3/p85 complexes in SNU638 and MKN45 gastric cancer cells, as well as H1993 NSCLC cells, which are known to harbor an amplified *MET* allele (Fig. 3A). In all cases, the ERBB3/p85 complexes could be disrupted by PHA-665752 but not by gefitinib, lapatinib (a dual EGFR/ERBB2 inhibitor), or CL-387,785 (an irreversible EGFR/ERBB2 inhibitor). Accordingly, phosphorylation of ERBB3 and Akt was inhibited only by PHA-665752 but not by the other compounds (Fig. 3A). Finally, *ERBB3*-specific shRNAs also resulted in a marked decrease in phosphorylation of Akt (Fig. 3B) and significantly inhibited cell growth of SNU-638 cells (Fig. 3C). Thus, we conclude that *MET* amplification leads to ERBB3 phosphorylation and PI3K activation in an EGFR- and ERBB2-independent manner. More generally, these studies suggest that ERBB3-mediated activation of PI3K/Akt might be a common feature of cancer cells that have *MET* amplification.

To investigate how MET activates ERBB3 tyrosine phosphorylation, we first expressed ERBB3 alone or in combination with MET in

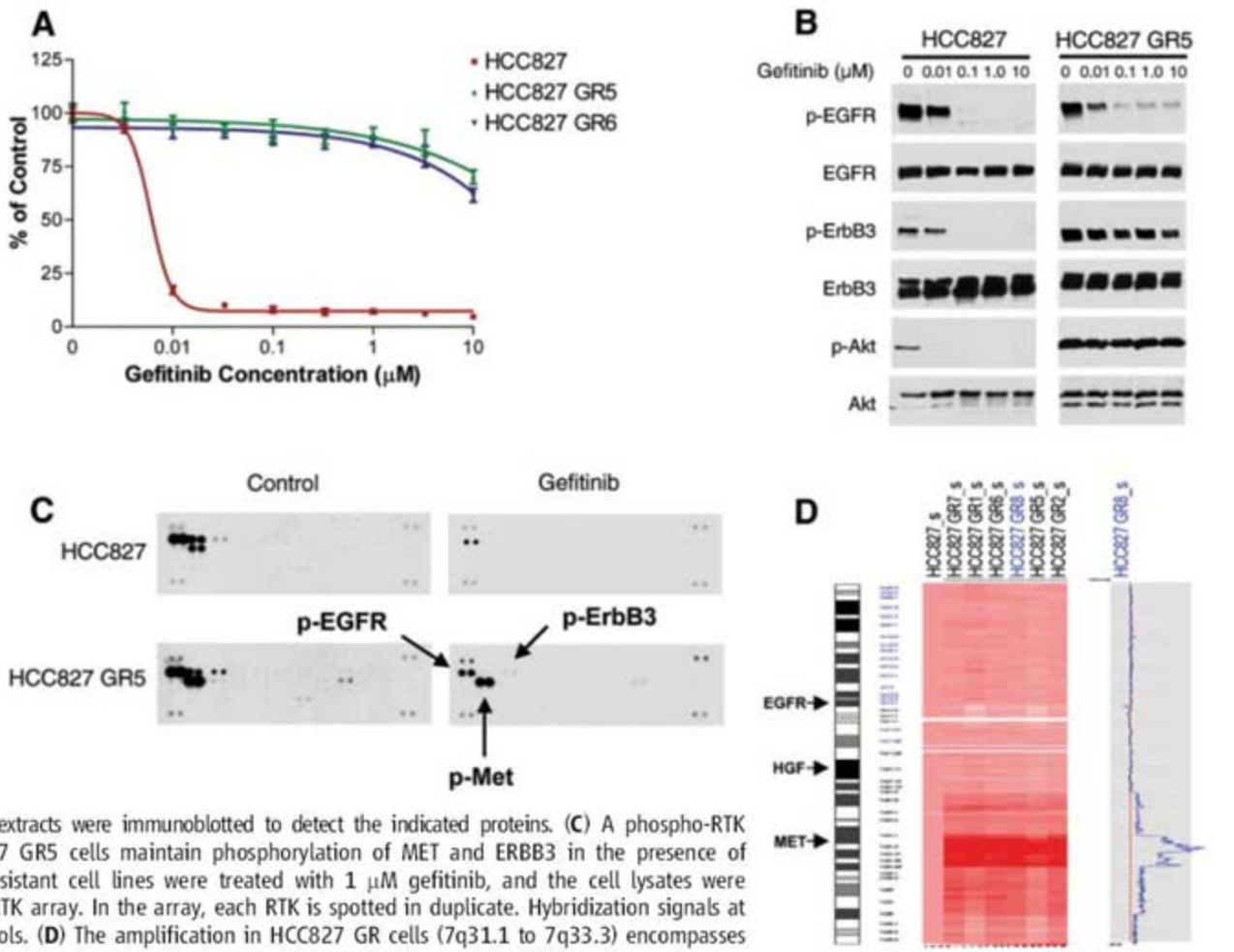

Fig. 1. HCC827 GR cells are resistant to gefitinib in vitro and show *MET* amplification. (**A**) The *EGFR* mutant HCC827 human lung cancer cell line was made resistant to gefitinib by growing it in increasing concentrations of gefitinib (*8*). Parental and resistant HCC827 GR5 and GR6 cells were treated with gefitinib at the indicated concentrations, and viable cells were measured after 72 hours of treatment. The percentage of viable cells is shown relative to untreated controls. (**B**) Gefitinib-resistant cells maintain ERBB3 and Akt phosphorylation in the presence of gefitinib. HCC827 and HCC827 GR5 cells were exposed to increasing concentrations of gefitinib for 6 hours. Cell extracts were immunoblotted to detect the indicated proteins. (**C**) A phospho-RTK array reveals that HCC827 GR5 cells maintain phosphorylation of MET and ERBB3 in the presence of gefitinib. Parental and resistant cell lines were treated with 1 μM gefitinib, and the cell lysates were hybridized to a phospho-RTK array. In the array, each RTK is spotted in duplicate. Hybridization signals at the corners serve as controls. (**D**) The amplification in HCC827 GR cells (7q31.1 to 7q33.3) encompasses *MET* but not *HGF*, the gene encoding its ligand hepatocyte growth factor, or the *EGFR* gene.

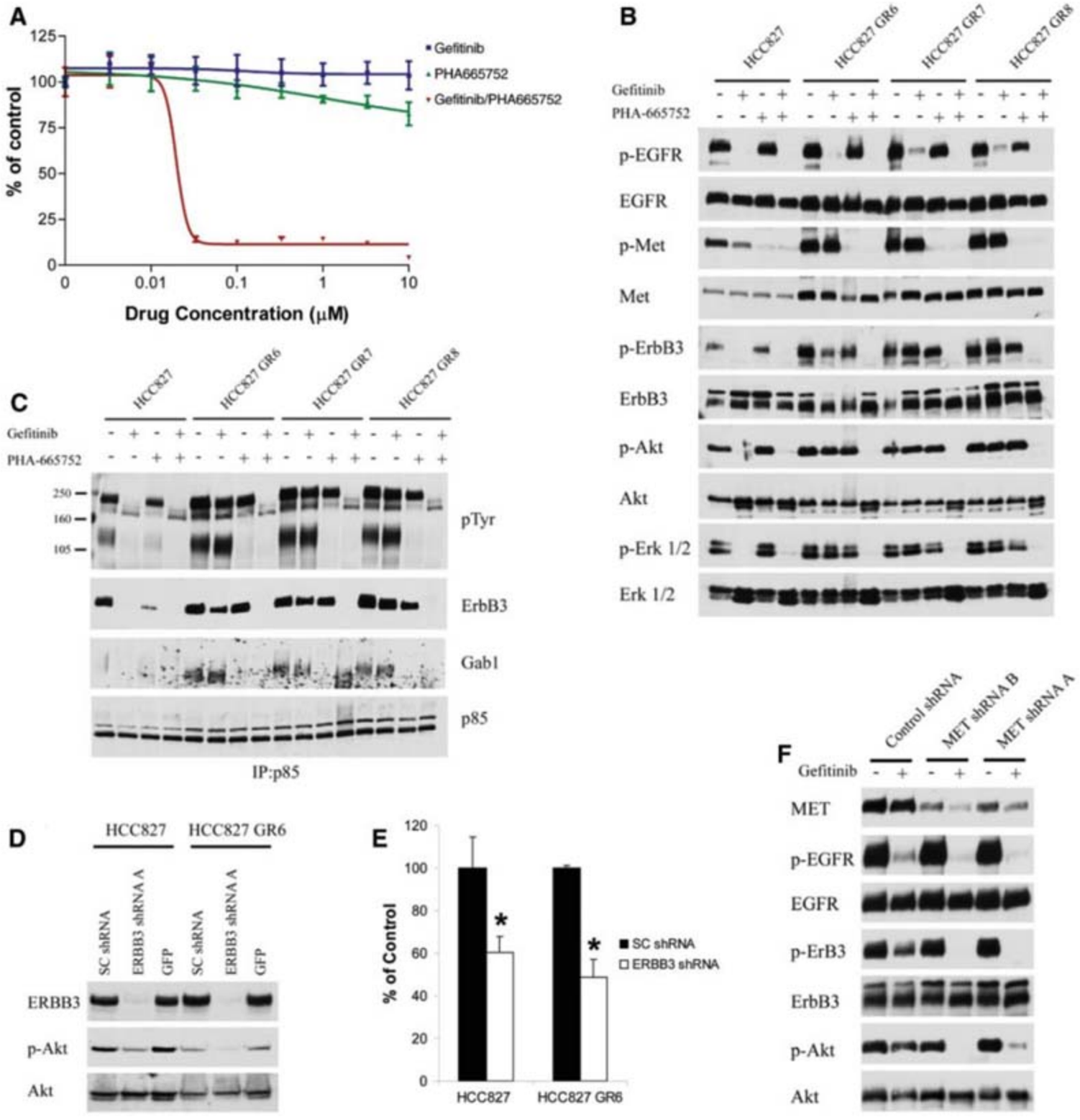

Fig. 2. Concurrent inhibition of MET and EGFR suppresses growth of HCC827 GR cells and leads to down-regulation of ERBB3/PI3K/AKT signaling. (**A**) The HCC827 GR5 cells were treated with increasing concentrations of gefitinib alone, PHA-665752 alone, or the two drugs in combination. Growth was assessed by the MTS survival assay. (**B**) The phosphorylation of ERBB3, Akt, and MET is substantially reduced only by the combination of gefitinib and PHA-665752 in the resistant cells. Parental and resistant cells were treated for 6 hours with gefitinib alone, the MET inhibitor PHA-665752 alone, or the two drugs in combination. Cells were lysed, and the indicated proteins were detected by immunoblotting. (**C**) The association of ERBB3 with p85 is blocked only by the combination of gefitinib and PHA-665752 in the resistant cells. Parental and resistant cells were treated as in (B). Cell extracts were immunoprecipitated with an antibody to p85. The precipitated proteins were determined by immunoblotting with the indicated antibodies. (**D**) Down-regulation of ERBB3 by an *ERBB3*-specific shRNA results in loss of Akt phosphorylation in both HCC827 and HCC827 GR6 cells. Control or *ERBB3*-specific shRNAs were introduced into parental or resistant cells. Cell extracts were prepared 96 hours later and immunoblotted with the indicated antibodies. SC, scrambled; GFP, green fluorescent protein. (**E**) The viability of cells from (D) was measured using an MTS assay. Viability of cells expressing the *ERBB3*-specific shRNA is shown relative to cells expressing control shRNA. Error bars indicate SD. *, $P < 0.05$ (paired *t* test). (**F**) Down-regulation of MET by *MET*-specific shRNAs restores gefitinib-induced down-regulation of ERBB3 and Akt phosphorylation. Control or *MET*-specific shRNAs were introduced into HCC827 GR6 cells. The cells were treated with 1 μM gefitinib, and cell extracts were immunoblotted with indicated antibodies.

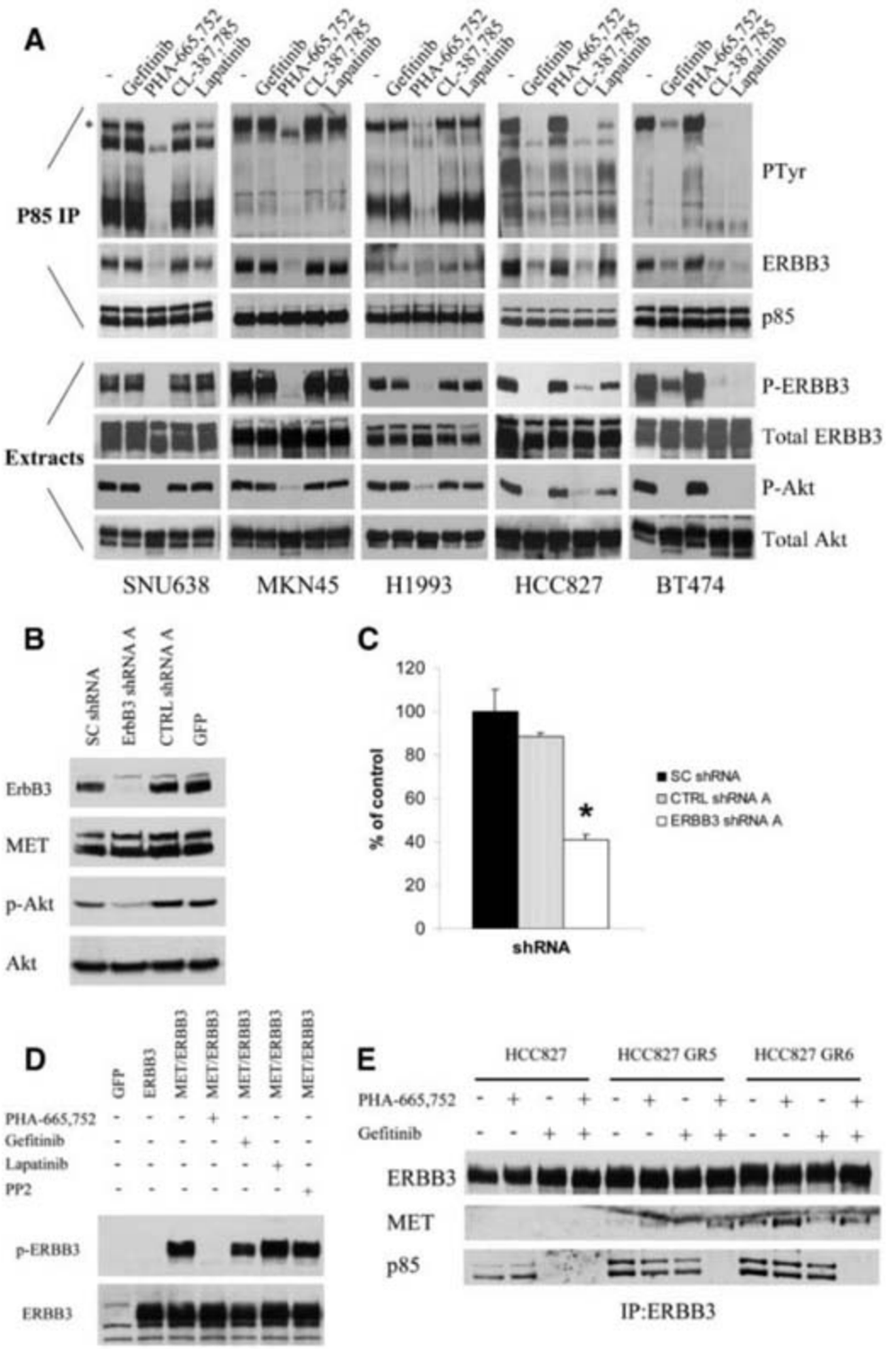

Fig. 3. MET activates ERBB3/PI3K signaling in tumor cell lines with *MET* amplification. (**A**) *MET*-amplified cell lines (with wild-type *EGFR*) also use ERBB3 to activate PI3K/Akt signaling. Cell lines with *MET* amplification (gastric cancer cell lines, SNU-638 and MKN-45, and the NSCLC cell line H1993), with an *EGFR* mutation (NSCLC cell line HCC827), or with *ERBB2* amplification (breast cancer cell line BT474) were treated with the indicated drugs for 6 hours. Cell extracts were immunoprecipitated with an antibody to p85. The precipitated proteins were determined by immunoblotting with the indicated antibodies. In parallel, whole-cell extracts were immunoblotted to detect the indicated proteins. *, ERBB3. (**B**) Down-regulation of ERBB3 by an *ERBB3*-specific shRNA results in loss of Akt phosphorylation in SNU-638 cells. SC, scrambled; GFP, green fluorescent protein; CTRL, control. (**C**) The viability of cells from (B) was measured using an MTS assay. *, $P < 0.05$ (paired t test). (**D**) MET induces ERBB3 phosphorylation. cDNAs encoding for *GFP*, *ERBB3*, or *MET* were introduced into CHO cells. The cells were treated with the indicated drugs for 6 hours, and cell extracts were immunoblotted to detect indicated proteins. (**E**) ERBB3 coprecipitates with MET and p85 from the resistant but not the parental HCC827 cells. HCC827 and HCC827 GR cells were treated with gefitinib alone, PHA-665752 alone, or both drugs in combination. Cell extracts were immunoprecipitated with an antibody to ERBB3. The precipitated proteins were identified by immunoblotting with the indicated antibodies.

Chinese hamster ovary (CHO) cells, which normally do not express detectable levels of EGFR, ERBB2, or ERBB3. Coexpression of MET and ERBB3 resulted in marked phosphorylation of ERBB3 (Fig. 3D). This phosphorylation could be blocked with PHA-665752 but not with high concentrations of gefitinib (3 μM), lapatinib (3 μM) or the SRC family kinase inhibitor PP2 (10 μM). In addition, phosphorylated ERBB3 coimmunoprecipitated with p85 in a MET kinase–dependent manner (fig. S6). We also found that endogenous ERBB3 coprecipitates with MET and p85 in the HCC827 GR cells (Fig. 3E). Similarly, the interaction between ERBB3 and p85 was blocked only with the combination of gefitinib and PHA-665752 in the resistant cells.

To assess the clinical relevance of this resistance mechanism, we examined whether *MET* amplification could be detected in *EGFR* mutant NSCLCs that had become resistant to gefitinib. We analyzed tumors from 18 patients (tables S2 and S3), all of whom had shown partial response to gefitinib or erlotinib during initial treatment but showed signs of tumor regrowth (i.e., resistance) while still receiving these drugs. *MET* copy status was assessed either by quantitative PCR when only tumor-derived DNA was available ($n = 11$) or by fluorescence in situ hybridization (FISH) when tumor sections were available ($n = 7$) (fig. S7). For eight patients, we were able to obtain paired tumor specimens from before treatment and after the development of resistance to gefitinib. For the other 10 patients, tumor specimens were available only after the development of resistance to gefitinib or erlotinib. Overall, *MET* amplification was detected in 4 out of 18 (22%) gefitinib/erlotinib–resistant tumor specimens. Of the eight paired tumor samples, two showed *MET* amplification in the resistant specimens but not in the before-treatment samples. In patient 1, the level of *MET* amplification in the post-treatment specimen was similar to that observed in the HCC827 GR cell lines (table S2 and fig. S2). *MET* amplification was also detected in two other patients for whom only post-treatment specimens were available (patients 12 and 13). Of the four resistant tumors with *MET* amplification, one had a concurrent *EGFR* T790M mutation; the other three did not. Interestingly, two independent resistant tumors from patient 12 were analyzed, and one had an *EGFR* T790M while the other had a *MET* amplification (table S2).

Mechanisms of acquired resistance to kinase inhibitors in NSCLC, chronic myelogenous leukemia (CML), and gastrointestinal stromal tumor include secondary mutations in the kinase itself (*EGFR*, *KIT*, or *BCR-ABL*), amplification of the target kinase (*KIT* or *BCR-ABL*), or overexpression of other kinases downstream of the target kinase (for example, *LYN* in CML) (*5*, *16*–*19*). However, *MET* amplification provides an example of a resistance mechanism characterized by

gene amplification of a kinase that is not a direct or downstream target of gefitinib or erlotinib. Moreover, MET has not previously been shown to signal through ERBB3. These findings may have important clinical implications for NSCLC patients who develop acquired resistance to gefitinib or erlotinib. Our findings also suggest that irreversible EGFR inhibitors, which are currently under clinical development as treatments for patients whose tumors have developed acquired resistance to gefitinib and erlotinib, may be ineffective in the subset of tumors with a *MET* amplification even if they contain an *EGFR* T790M mutation. Therefore, combination therapies with MET kinase inhibitors, which are in early-stage clinical trials, and irreversible EGFR inhibitors should be considered for patients whose tumors have become resistant to gefitinib or erlotinib. Notably, a small percentage of NSCLCs from EGFR TKI–naïve patients have been reported to contain both an *EGFR*-activating mutation and *MET* amplification (*20*, *21*). This situation is analogous to the observation that untreated NSCLCs occasionally have an *EGFR* T790M. These concurrent genetic alterations may help explain why some NSCLCs with *EGFR*-activating mutations fail to respond when initially treated with gefitinib (*22*).

It will continue to be important to study NSCLC primary tumors and cell lines with acquired resistance to EGFR inhibitors for insights into additional resistance mechanisms. Our findings illustrate the value of studying genetic alterations that produce persistent PI3K/Akt signaling in the presence of gefitinib rather than focusing solely on mutations in the *EGFR* gene itself. It will also be important to determine whether *MET* amplification contributes to resistance in other *EGFR*-dependent cancers such as glioblastoma multiforme, head and neck cancer, and colorectal cancer after treatment with EGFR-directed therapies. Finally, since ERBB2-amplified breast cancers also activate PI3K/Akt signaling through ERBB3, it will be interesting to explore whether *MET* amplification also occurs in breast cancers that develop resistance to drugs that target ERBB2, such as trastuzumab and lapatinib (*9*, *23*).

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Supporting Online Material

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Materials and Methods
Figs. S1 to S7
Tables S1 to S4
References

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Wilms Tumor Suppressor WTX Negatively Regulates WNT/β-Catenin Signaling

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Aberrant WNT signal transduction is involved in many diseases. In colorectal cancer and melanoma, mutational disruption of proteins involved in the degradation of β-catenin, the key effector of the WNT signaling pathway, results in stabilization of β-catenin and, in turn, activation of transcription. We have used tandem-affinity protein purification and mass spectrometry to define the protein interaction network of the β-catenin destruction complex. This assay revealed that WTX, a protein encoded by a gene mutated in Wilms tumors, forms a complex with β-catenin, AXIN1, β-TrCP2 (β-transducin repeat–containing protein 2), and APC (adenomatous polyposis coli). Functional analyses in cultured cells, *Xenopus*, and zebrafish demonstrate that WTX promotes β-catenin ubiquitination and degradation, which antagonize WNT/β-catenin signaling. These data provide a possible mechanistic explanation for the tumor suppressor activity of WTX.

In the absence of WNT ligands, cytosolic β-catenin is constitutively degraded through phosphorylation-dependent ubiquitination and subsequent proteosomal clearance. A complex of proteins including adenomatous polyposis coli (APC), AXIN, casein kinase 1α (CK1α), and glycogen synthase kinase 3 (GSK3) phosphorylates N-terminal serine residues in β-catenin, which creates a substrate efficiently ubiquitinated by the Skp1, Cullin1, F-box protein β-TrCP ($SCF^{\beta TrCP}$) ubiquitin ligase (*1*). The engagement of a Frizzled receptor with WNT ligand initiates a signaling cascade, culminating in the inactivation of the β-catenin destruction complex. Consequently, β-catenin levels increase in the nucleus, where it functions as a transcriptional coactivator for members of the TCF-LEF family of transcription factors (*2*, *3*). Although mutations in APC are common in colorectal cancer, many human malignancies harboring active WNT/β-catenin signaling have no identified causative mutation(s) (*4*, *5*).

To identify proteins associated with the β-catenin destruction complex, we performed a tandem-affinity purification (TAP) of $\beta\text{-catenin}^{(SA)}$, AXIN1, APC (amino acids 1 to 1060), β-TrCP1, and β-TrCP2 in mammalian cells (*6*). The $\beta\text{-catenin}^{(SA)}$ mutant has alanine substituted for serine at codon 37. Specifically, cDNA for each of these "bait" proteins was cloned into the pGlue vector encoding a dual-affinity tag containing streptavidin-binding protein (SBP), calmodulin-binding protein (CBP), and the hemagglutinin (HA) epitope (*7*). Lines of human embryonic kidney cells (HEK293T) expressing low levels of each of the tagged-bait fusion proteins were generated, then detergent-solubilized, subjected to two rounds of affinity purification, trypsinized,

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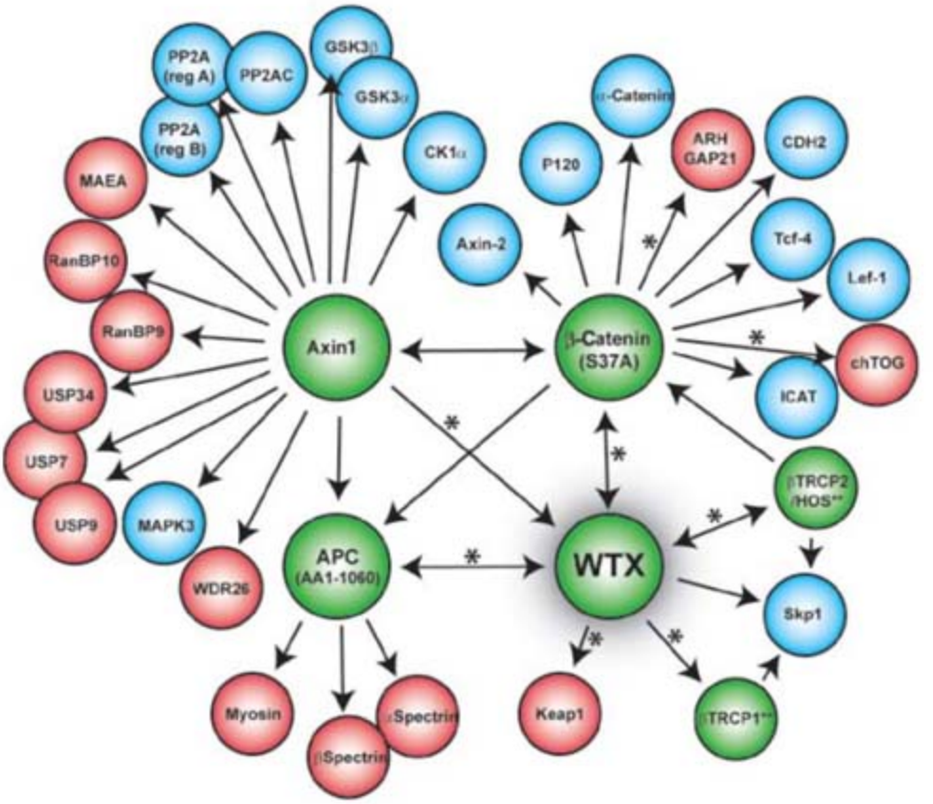
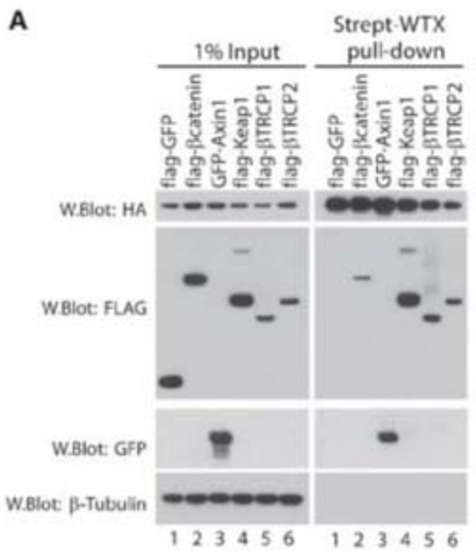
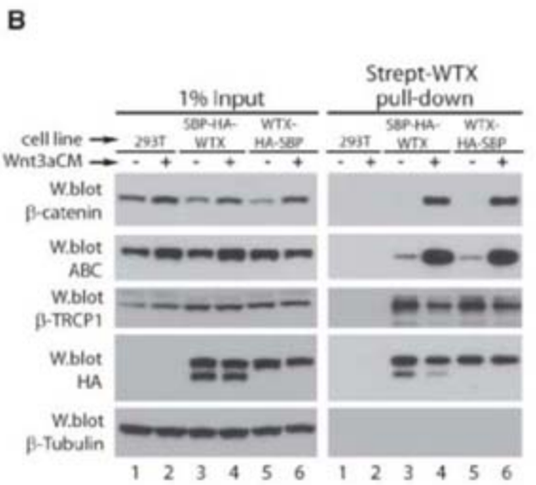
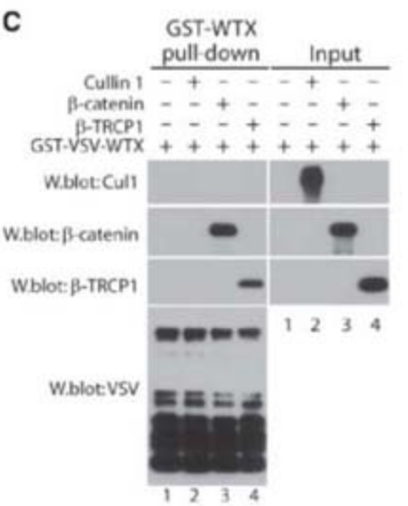
Fig. 1. The β-catenin protein interaction network. Green circles represent proteins used as bait in the tandem affinity purification, blue circles represent known interactors, and red circles represent novel interactors. The arrows indicate directionality for the bait-interactor discovery, and the single asterisks (*) show interactions that were confirmed in secondary assays. **The protein interaction networks for β-TrCP1 and β-TrCP2 are not yet complete.









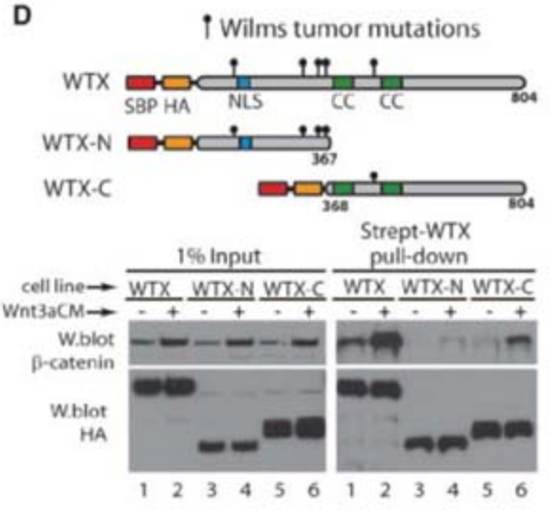


Fig. 2. WTX directly binds the β-catenin destruction complex. (**A**) WTX associates with ectopically expressed β-catenin, AXIN1, β-TrCP1, β-TrCP2, and Keap1. FLAG-tagged proteins were transiently expressed in HEK293T cells stably expressing SBP-HA-WTX. Protein lysates were subjected to streptavidin affinity pull-down followed by Western blot analysis. (**B**). WTX associates with endogenous β-catenin and β-TrCP1. Parental HEK293T cells or HEK293T cells stably expressing N-terminal or C-terminal pGlue-WTX were treated with WNT3a-conditioned medium (CM) for 2 hours before lysis, streptavidin-affinity pull-down assay, and Western blot analysis (ABC, active β-catenin). (**C**) WTX directly binds β-catenin and β-TrCP1. GST–vesicular stomatitis virus (VSV)–WTX recombinant protein was incubated with recombinant Cul1, β-catenin, or β-TrCP at equal molar ratios. After GST affinity purification, protein complexes were washed with buffered 350 mM NaCl before associated proteins were resolved by Western blot. (**D**) WTX protein sequences C-terminal to the region mutated in Wilms tumors bind β-catenin. (Top) The cartoon illustrates the location of missense mutations found in Wilms tumors, as well as the N-terminal and C-terminal WTX expression constructs used to create HEK293T stably expressing cell lines. WNT3a CM treatment, affinity pull-down assay, and Western blotting were performed as in (B).

and analyzed by liquid chromatography–tandem mass spectrometry (LC-MS/MS). The resulting data for all bait proteins were integrated to yield the protein-protein interaction network of the β-catenin destruction complex (Fig. 1 and table S1). This proteomic analysis confirmed the presence of all the core proteins identified in previous screens (*1*), including β-catenin, APC, AXIN1, AXIN2, protein phosphatase PP2A, GSK3α, GSK3β, and CK1α. In addition, 13 new proteins were found to associate with known components of the destruction complex.

We further explored WTX (FLJ39287/FAM123B) because it copurified with each of the baits examined. The WTX gene was recently discovered to be mutated in ~30% of Wilms tumors, which are pediatric kidney cancers (*8*). Constitutive activation of WNT/β-catenin signaling is common in Wilms tumors; ~10% of tumors harbor activating mutations in β-catenin (*9*), and nuclear β-catenin is observed in ~50% of tumors lacking detectable β-catenin mutations (*10*). Note that WTX and β-catenin mutations were mutually exclusive in the tumor samples examined (*8*).

To test the hypothesis that WTX negatively regulates WNT/β-catenin signaling in normal kidney, we generated HEK293T cells that stably express pGlue-WTX (supporting online text). From these cells, we isolated and identified WTX-associated protein complexes by TAP/LC-MS/MS (Fig. 1 and table S1). β-Catenin and β-TrCP were among the most abundant WTX-interacting proteins, which independently confirms the interactions of β-catenin$^{(SA)}$–WTX and β-TrCP2–WTX. To validate the WTX protein interaction network, we assessed protein binding in HEK293T cells and in vitro. We transiently expressed FLAG-tagged fusion proteins in cells stably expressing pGlue-WTX, isolated WTX by streptavidin affinity chromatography, and detected bound FLAG-tagged fusion proteins by Western blot (Fig. 2A). The reverse pull-down strategy yielded identical results (fig. S1). These data demonstrate that WTX binds both wild type β-catenin and the stabilized β-catenin$^{(SA)}$ mutant (Fig. 2A and fig. S1).

Using cells stably expressing either N-terminal or C-terminal tagged WTX, we next investigated whether endogenous proteins within the destruction complex bound WTX. Streptavidin affinity purification of WTX revealed that it associates with endogenous β-catenin and β-TrCP (Fig. 2B and supporting online text). Additionally, using purified recombinant protein in vitro, we found that WTX directly binds β-catenin and β-TrCP1, but not the Cullin1 scaffold within the E3 ligase complex (Fig. 2C). These results show that post-translational modifications are not required for WTX binding to β-catenin or β-TrCP1.

Although deletion of the *WTX* gene was more commonly found in Wilms tumor samples, five truncating mutations were identified in tumors within the amino-terminal half of the protein (*8*). As such, these mutations are consistent with the existence of a putative tumor suppressor motif within the C terminus of WTX. If WTX regulates

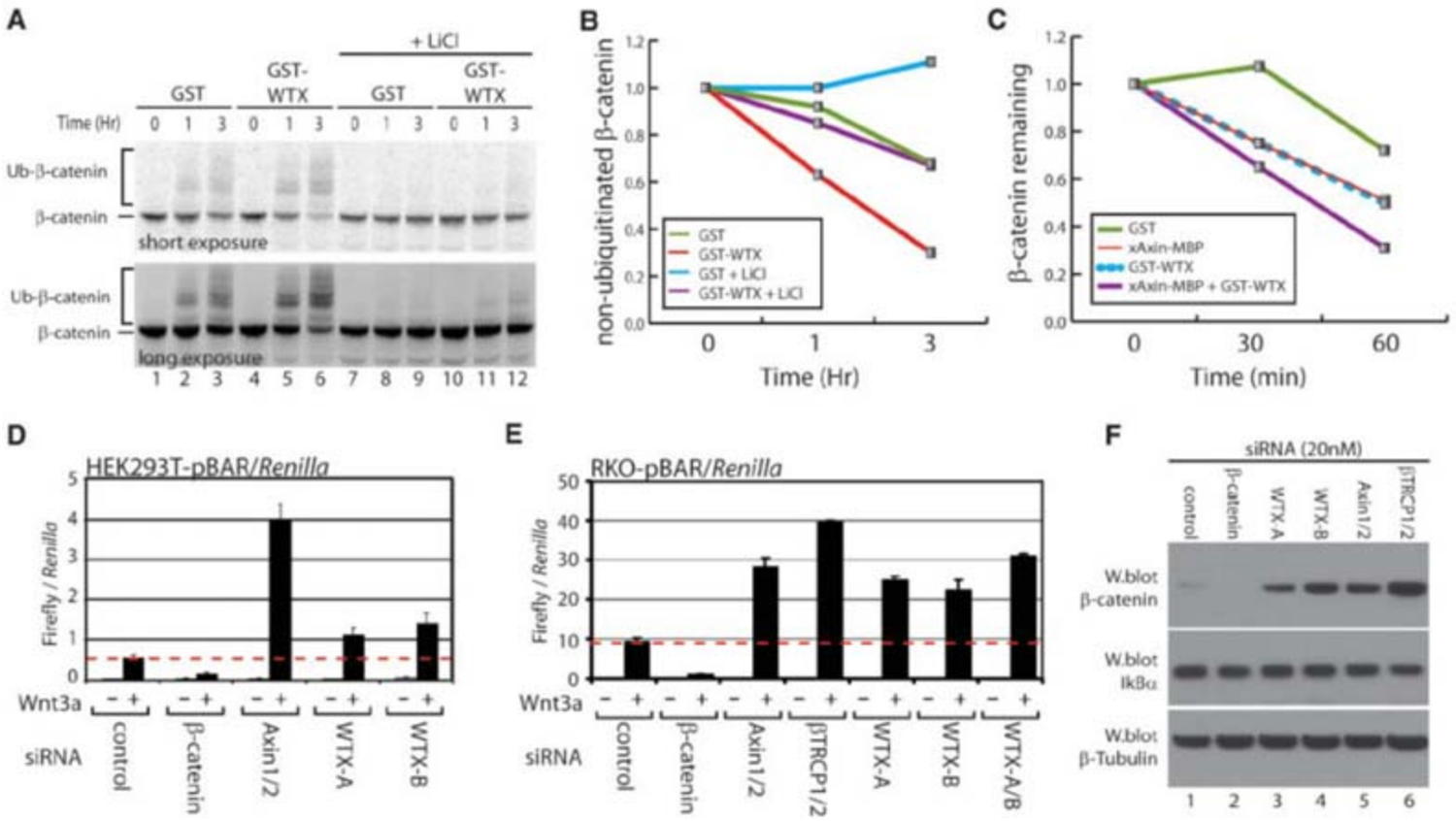


Fig. 3. WTX promotes β-catenin ubiquitination and degradation. (**A**) A cell-free system of *Xenopus* egg extracts was used to monitor β-catenin ubiquitination as a function of time. In vitro transcribed and translated ^{35}S-labeled β-catenin was added to *Xenopus* egg extracts in the presence of methylated ubiquitin (MeUb) and either purified GST or GST-WTX protein. Measuring the extent of ^{35}S-labeled β-catenin ubiquitination was followed by SDS–polyacrymamide gel electrophoresis (SDS-PAGE) and autoradiography. As a measure of specificity, LiCl (10 mM) was added to inhibit β-catenin phosphorylation and subsequent ubiquitination. (**B**) Quantification of nonubiquitinated ^{35}S-labeled β-catenin levels from (A). (**C**) Recombinant GST-WTX and myelin basic protein (MBP)–AXIN1 synergize to degrade ^{35}S-labeled β-catenin in *Xenopus* egg extracts. Graphic representation of ^{35}S-labeled β-catenin degradation as a function of time; note absence of methylated ubiquitin (meUb) in this experiment, as well as difference in time scale. (**D** and **E**) WTX silencing synergizes with WNT3a CM to activate a β-catenin–responsive luciferase reporter (pBAR) in mammalian cells. HEK293T cells (D) or RKO cells (E) stably expressing the pBAR reporter and *Renilla* luciferase were transiently transfected with siRNAs targeting the indicated mRNAs. Two days after transfection, cells were treated with control or WNT3a CM for 14 hours. BAR-luciferase values were normalized to *Renilla* and plotted. Error bars represent standard deviation from the mean. Data are representative of 4 independent experiments for HEK293T cells and 12 independent experiments for RKO cells. (**F**) WTX silencing stabilizes β-catenin. RKO cells were transfected with siRNAs targeting the indicated mRNAs. Two days after transfection, cells lysates were subjected to Western blot analysis for the indicated proteins. IκBα, inhibitor of nuclear factor κB and a β-TrCP substrate induced by tumor necrosis factor–α stimulation, as well as β-tubulin, demonstrate equal protein loading in the blots.

kidney biology through negative regulation of WNT/β-catenin signaling, then we should be able to ascribe a WNT-related function to the C terminus of WTX. Therefore, we mapped the domain of WTX that interacts with β-catenin and found that β-catenin purified with full-length WTX and the C-terminal half of WTX (WTX-C), but interacted poorly with the N-terminal half (WTX-N) (Fig. 2D and fig. S2 and supporting online text). As additional confirmation, we used our TAP–LC-MS/MS analysis on cells expressing pGlue–WTX-C and found both β-TrCP and β-catenin within the protein complex (table S1). Thus, mutational alteration of WTX in Wilms tumor likely reduces its interaction with β-catenin and β-TrCP.

The direct binding of WTX to both β-catenin and to its E3 ubiquitin ligase adaptor, β-TrCP, suggests that WTX regulates β-catenin degradation. We tested this hypothesis using cell-free *Xenopus* egg extracts, an experimental system that allows quantitative monitoring of β-catenin ubiquitination and degradation (*11*). The addition of recombinant glutathione *S*-transferase (GST) in complex with WTX protein increased the rate of β-catenin ubiquitination, but GST control did not (Fig. 3, A and B, and fig. S3). Inhibition of GSK3 by lithium chloride (LiCl) suppressed β-catenin ubiquitination in the presence of GST and GST-WTX. As a scaffold protein, AXIN nucleates the GSK3-CK1-APC phosphorylation complex and thereby dramatically increases β-catenin turnover in *Xenopus* extracts (*11*). When WTX and AXIN1 were added to the extracts individually, each increased the rate of β-catenin degradation (Fig. 3C). When WTX and AXIN1 were added together, the rate of β-catenin degradation was more rapid than observed with either alone. These data suggest that WTX negatively regulates WNT signaling by promoting β-catenin ubiquitination.

If WTX promotes β-catenin degradation, then suppressing WTX expression should activate WNT/β-catenin signaling in mammalian cells. To test this prediction, we measured the activity of a β-catenin–dependent transcriptional reporter after small interfering RNA (siRNA)-mediated silencing of *WTX*. Specifically, HEK293T human embryonic kidney cells and RKO human colon carcinoma cells were transduced with lentiviruses encoding a firefly luciferase–based β-catenin–activated reporter (pBAR), along with *Renilla* luciferase (*Renilla*-Luc) under the control of the constitutively active thymidine kinase promoter for normalization. To validate the dynamic range of this reporter system, stably transduced cell lines were treated with WNT3a-conditioned medium, which activated the reporter by a factor of 100 to 300 (Fig. 3, D and E). As a control, we showed that siRNAs directed against β-catenin abolished this WNT3a-induced reporter activity in both cell lines (fig. S4 and supporting online text). Using this assay system, we found that two different siRNAs targeting WTX produced an increase in WNT3a-induced reporter activity in both cell types. Furthermore, in RKO-pBAR/*Renilla* cells, siRNA-mediated silencing of WTX, AXIN1 and 2, or β-TrCP1 and 2 synergized with a GSK3 inhibitor, (2′*Z*,3′*E*)-6-bromoindirubin-3′-oxime, to activate the pBAR reporter (fig. S4). These data suggest that WTX is a negative regulator of WNT/β-catenin signal transduction in mammalian cells.

We next tested whether silencing of *WTX* with siRNAs increases β-catenin levels in cells. In RKO cells, β-catenin does not localize to the plasma membrane, whereas in other cell types, such as HEK293T cells, it resides with a relatively long half-life at the inner surface of the plasma membrane. Thus, in the absence of membrane-associated β-catenin, total cellular levels of β-catenin in RKO cells are very low, which allows study of cytoplasmic and nuclear β-catenin stability in response to experimental perturbation. We transiently transfected RKO cells with siRNAs targeting WTX, β-catenin, AXIN1 and 2, or β-TrCP1 and 2. Silencing of WTX, AXIN1 and 2, or β-TrCP1 and 2, but not β-catenin, was found to increase β-catenin levels, as determined by immunoblot analysis (Fig. 3F). Thus, WTX is required in these cells as a negative regulator of both β-catenin protein stability and β-catenin–mediated transcription.

To extend these experiments to organisms, we performed gain-of-function experiments in *Xenopus* embryos and loss-of-function experiments in zebrafish (supporting online text). Ectopic activation of WNT/β-catenin signaling by injection of *Xenopus Wnt8* mRNA in *Xenopus* embryo ventral blastomeres induced duplication of the embryonic axis, yielding two-headed tadpoles (fig. S5). Injection of *WTX* mRNA blocked *Xenopus Wnt8*–induced axis duplication. In developing zebrafish embryos, ectopic activation of WNT/β-catenin signaling leads to anterior truncations. When we silenced endogenous zebrafish wtx expression, we observed anterior truncations and the activation of a WNT/β-catenin reporter gene (fig. S5). These results suggest that WTX is a negative regulator of WNT/β-catenin signaling in vivo.

In summary, these data establish that the cancer-associated WTX protein is a required component of the β-catenin destruction complex. Furthermore, our data underscore the power of proteomic approaches for identifying new components of cellular signal transduction pathways that may ultimately provide important mechanistic insights into human disease.

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Supporting Online Material

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Revisiting the Role of the Mother Centriole in Centriole Biogenesis

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Centrioles duplicate once in each cell division cycle through so-called templated or canonical duplication. SAK, also called PLK4 (SAK/PLK4), a kinase implicated in tumor development, is an upstream regulator of canonical biogenesis necessary for centriole formation. We found that overexpression of SAK/PLK4 could induce amplification of centrioles in *Drosophila* embryos and their de novo formation in unfertilized eggs. Both processes required the activity of DSAS-6 and DSAS-4, two molecules required for canonical duplication. Thus, centriole biogenesis is a template-free self-assembly process triggered and regulated by molecules that ordinarily associate with the existing centriole. The mother centriole is not a bona fide template but a platform for a set of regulatory molecules that catalyzes and regulates daughter centriole assembly.

Centrioles are essential for the formation of cilia and flagella and for the organization of the centrosome (*1*). Normally, centrioles duplicate in coordination with the cell cycle. A new centriole, the daughter, arises orthogonally to each old one, the mother (*1*), in S phase. This led to the idea that the mother centriole templates the formation of the daughter (*2*, *3*). However, daughter centrioles do not incorporate a substantial proportion of the mother (*4*),

and centrioles can also form de novo when existing centrioles are naturally lost during development or are physically removed (*5*–*7*), questioning the idea of the mother centriole as a template.

SAK, also called PLK4 (SAK/PLK4), a kinase implicated in tumor development (*8*), is an upstream regulator of canonical centriole duplication and is necessary for centriole formation (*9*, *10*). The *Caenorhabditis elegans* ZYG-1 kinase, a homolog of SAK, is part of a conserved module of proteins, which also includes SAS-6 and SAS-4, necessary for the normal centriole duplication cycle (*11*–*16*). ZYG-1 is an upstream regulator in that process (*17*, *18*), a role consistent with formation of multiple centrioles in cultured cells following overexpression of active SAK kinase (*9*, *10*). The generation of multiple centrioles associated with high SAK expression also occurs physiologically in the olfactory mucosa (*19*). The *Drosophila* egg contains all the proteins necessary to make 2^{13} centriole pairs (centrosomes) (*20*). Centrioles are naturally eliminated from the oocyte cytoplasm in the course of development and provided to the egg in the form of the basal body of the sperm (*20*–*23*). Thus, we studied the consequences of overexpressing SAK in a cytoplasm that either contained centrioles (the embryo) or lacked them (the unfertilized egg).

Embryos overexpressing SAK did not develop (*24*) (fig. S1A and Fig. 1A) and were filled with free asters of microtubules not associated with spindles (Fig. 1, B and D, and fig. S1B). Those asters were focused around *Drosophila* pericentrin-like protein (D-PLP)–containing structures, a centriolar and pericentriolar material (PCM) marker (*25*) (fig. S1B). These centrosomes first appeared in 15- to 30-min-old embryos (Fig. 1B) and spread to fill the entire embryo after 2 to 3 hours (Fig. 1, C and D). The observed supernumerary centrosomes led to abnormal mitotic progression and impaired embryonic development, as observed previously upon microtubule depolymerization by colchicine treatment (*26*). To address the origins of those centrosomes, we examined the very early stages of embryonic development in embryos overexpressing SAK. Both the sperm aster around the incoming basal body and the first mitotic spindle were normal (Fig. 1E). However, at anaphase or telophase of the first mitosis, we observed more than two centrosomes at each pole (Fig. 1E), an indication of the onset of centrosome amplification. No other centrosomes were seen in the embryo at this stage. Moreover, we estimated that a minimum of 3700 centrosomes (equivalent to 12 duplication cycles) were present after 60 min in embryos overexpressing SAK. After 60 min, a wild-type embryo only showed 128 centrosomes. We observed duplicating centrioles in groups, suggesting they originated by duplication of a progenitor (Fig. 1, D and E, and fig. S1B). Thus, upon fertilization of eggs overexpressing SAK, the basal body of the sperm enters an environment that promotes accelerated canonical duplication, overriding any existing controls that would normally couple the centrosome and chromosome cycles.

Uncoupling between centrosome and chromosome cycles occurs when embryos are arrested in S-phase–like conditions (*27*, *28*). However,

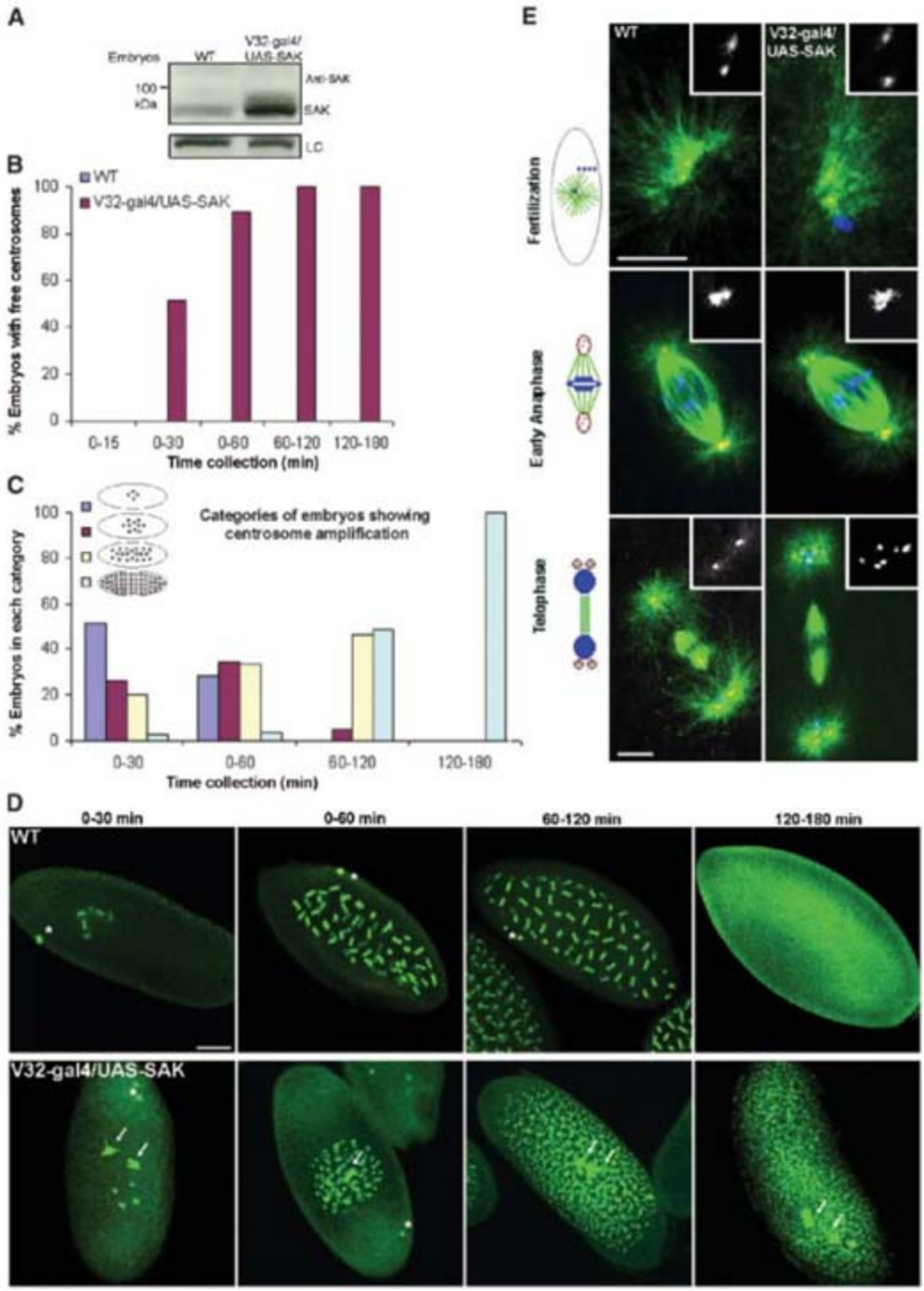

Fig. 1. Overexpression of SAK in *Drosophila* embryos leads to massive centrosome amplification. (**A**) Overexpression of upstream activation sequence (UAS)–SAK in embryos using the maternal driver V32-gal4. LC indicates loading control; WT, wild type. (**B**) Embryos overexpressing SAK become progressively full of free centrosomes nucleating asters. (**C** and **D**) The spreading of the centrosomes follows the wild-type spindle axial expansion pattern. Categories were as follows [according to the area occupied by the centrosomes within the embryo (*24*)]: 0 to 2%, 2 to 20%, 20 to 60%, and more than 60% area occupancy. α-tubulin is shown in green. An average of 60 embryos were counted in each category. Asterisks indicate polar bodies. Arrows indicate spindles. Scale bar indicates 50 μm. (**E**) Centrosome amplification in embryos is observed at the end of first mitosis. γ-tubulin is shown in red; α-tubulin, green; and DNA, blue. Scale bar, 10 μm. (Insets) γ-tubulin at 2×.

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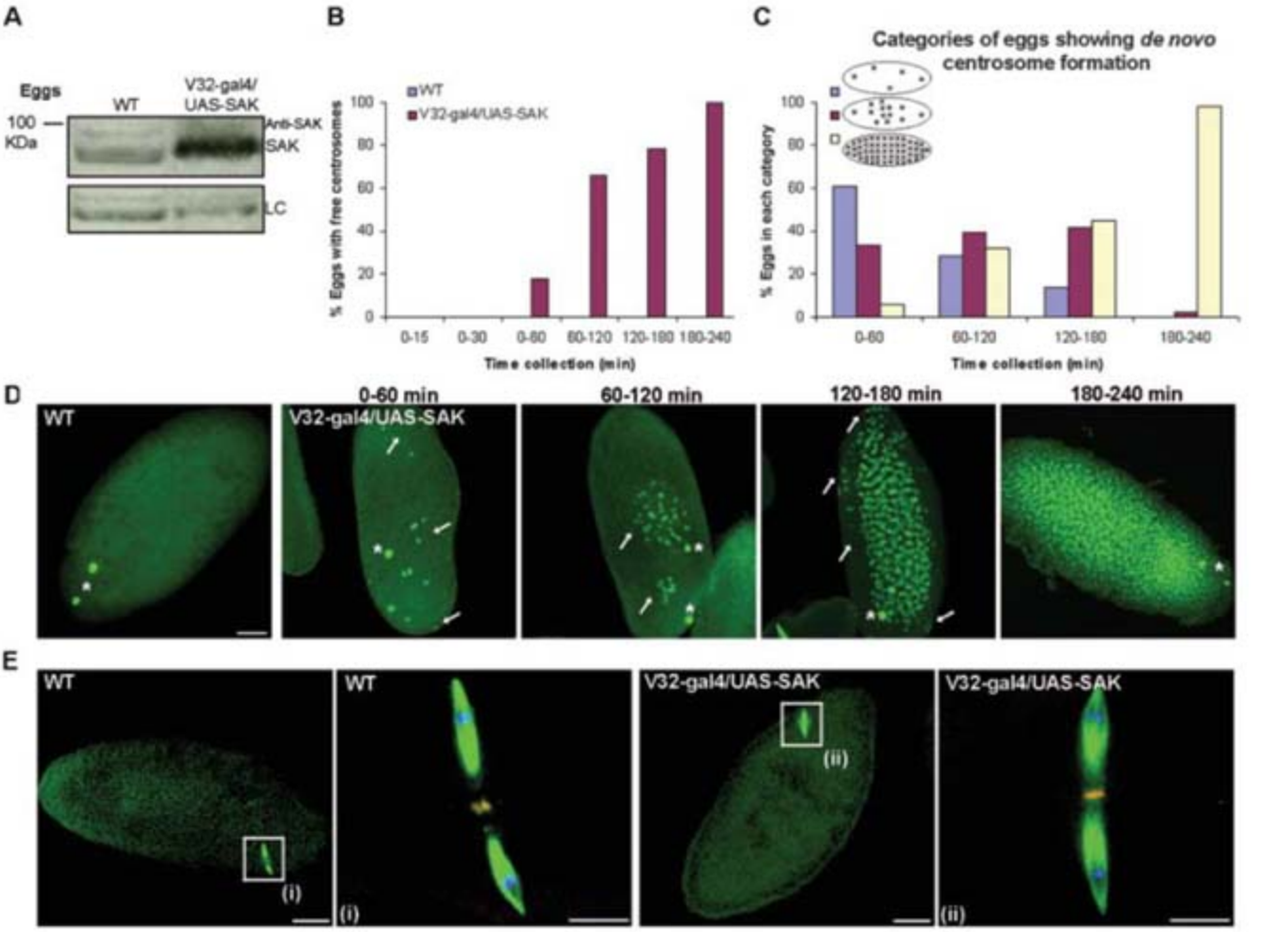

Fig. 2. SAK induces de novo centrosome formation in *Drosophila* eggs. (**A**) Overexpression of UAS-SAK in eggs using the maternal driver V32-gal4. LC, loading control. (**B**) De novo centrosome formation starts after 30 min. (**C** and **D**) De novo centrosomes appear randomly in space [arrows in (D)]. Categories were as follows: 0 to 2%, 2 to 60%, and more than 60% area occupancy. An average of 67 eggs was counted in each category. Scale bar, 50 μm. (**E**) Meiosis II occurs normally in V32-gal4/UAS-SAK eggs with no visible centrosomes (n = 110). i and ii indicate magnified fields. Scale bars, 50 μm (left) and 10 μm (inset) in each wild-type and overexpressing set. γ-tubulin, red; α-tubulin, green; and DNA, blue.

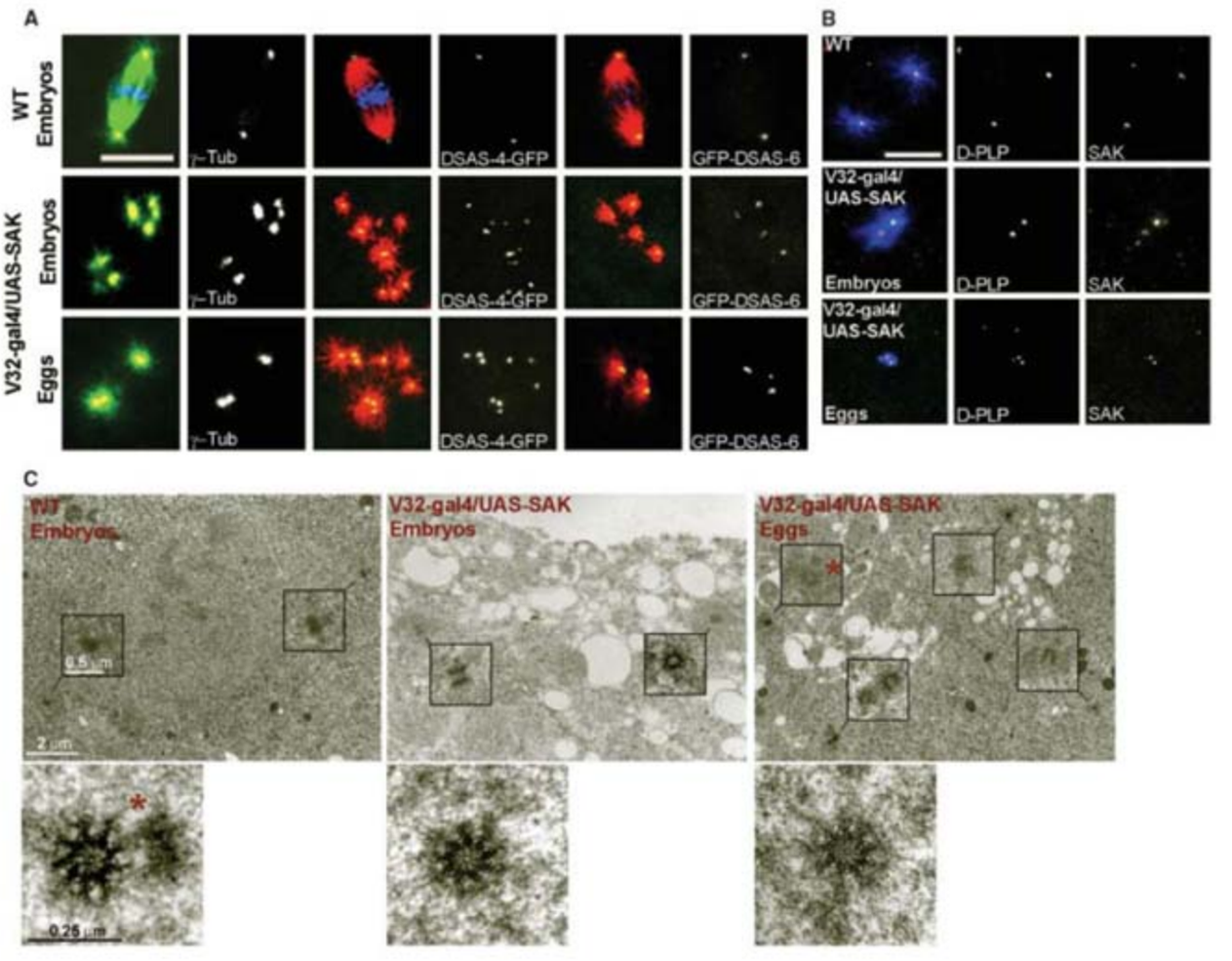

Fig. 3. De novo– and canonical-formed centrosomes show centriolar and centrosomal markers and are structurally normal. (**A** and **B**) Centrosomes in both 0 to 1 hour embryos and eggs overexpressing SAK contain γ-tubulin, DSAS-6, DSAS-4, and SAK. (A) γ-tubulin, red; α-tubulin, green in left and red in middle and right; green fluorescent protein (GFP)–DSAS6, green; DSAS4-GFP, green; and DNA, blue. Scale bar, 10 μm. (B) SAK, green; D-PLP, red; and α-tubulin, blue. Scale bar, 10 μm. (**C**) De novo– and canonical-formed centrosomes are structurally normal by transmission electron microscopy. Bottom images are higher-magnification examples of centrioles in each condition. Asterisks indicate duplicating centrioles. Scale bars as indicated.

this did not seem to be so in this case, because proliferating cell nuclear antigen (PCNA) (*29*), which appears early in S phase, was not detected in DNA of SAK-overexpressing embryos (fig. S2).

We next asked whether SAK could promote centriolar assembly in the absence of centrioles. Centrioles were lost normally in oocytes overexpressing SAK (fig. S3). Yet observations of unfertilized eggs at varying developmental intervals revealed free centrosomes in eggs overexpressing SAK that had exited meiosis II (Fig. 2 and fig. S4) but never in wild-type eggs. Thus, in the absence of a basal body provided by the sperm, SAK can induce de novo formation of centrosomes. Whereas in embryos centrosomes appeared in a single cluster in the first mitotic spindle and spread throughout the cytoplasm (Fig. 1, D and E), in unfertilized eggs they appeared scattered at random positions, including at the anterior and posterior poles (Fig. 2D, arrows). The formation of the first centrioles started later in eggs than in embryos [at 30 min, 0 amplification in eggs versus 51% amplification in embryos; after 1 hour, the amounts were 18% versus 89%, respectively (Figs. 1B and 2B and fig. S5)], suggesting that centrioles take longer to be made in the absence of a template. However, once the first centrosomes had formed in eggs, their spreading in space and time was very similar to that seen in embryos (compare Fig. 1D and Fig. 2D), indicative of canonical biogenesis. Thus, once the first centrioles are formed de novo, they probably duplicate through the canonical pathway.

There is precedent for defects in de novo–formed centrioles (*5*, *30*). We confirmed the presence of SAK (fig. S7) and two other molecules required for centriole duplication: DSAS-6 (fig. S6) (*31*) and DSAS-4 (*16*) (Fig. 3, A and B). We also detected PCM components, including γ-tubulin (Fig. 3A), centrosomin (CNN), and centrosomal protein 190 (CP190) (fig. S8, A and B). Moreover, electron microscopy showed that centrioles in both embryos and eggs overexpressing SAK were structurally normal (Fig. 3C). It also showed the presence of procentrioles next to the completed ones in both embryos and eggs (fig. S9 and Fig. 3C), a result suggesting that SAK-induced centrioles can duplicate.

Our results show that SAK is sufficient to induce both canonical and de novo centriole biogenesis. If both rely on self-assembly of the structure, we would predict the use of the same regulatory molecules. We examined the dependency of SAK-promoted centriole biogenesis on DSAS-4 and DSAS-6. We took advantage of the fact that centrioles can be eliminated from *Drosophila* tissue culture cells (*10*). After depletion of SAK in four rounds of RNA interference (RNAi) over a period of 16 days, more than 80% of the cells lacked centrioles, presumably because the remainder are diluted in each division cycle (Fig. 4A) (*10*). Subsequent overexpression of SAK led to a clear increase in the number of cells with several centrosomes (from 4 to 48%) (Fig. 4, A and B). Depletion of DSAS-6 or DSAS-4 prevented SAK-induced centrosome biogenesis in cells with and without centrioles (Fig. 4, A to C, and fig. S10).

Our results suggest that centriole biogenesis is a template-free self-assembly process that is locally triggered and regulated by molecules such as SAK, DSAS-6, and DSAS-4. What could be the role of the mother centriole? The presence of SAK at the centriole (Fig. 3B and fig. S7) (*9*, *10*) and the fact that assembly is faster in the presence of centrioles (fig. S5) (*5*, *6*) suggest that the mother centriole is not a bona fide template but a platform for regulatory molecules, hence catalyzing and regulating daughter centriole assembly. The establishment of that platform is probably less efficient in the absence of centrioles. The mother centriole could in principle establish a temporally and spatially regulated gradient of SAK activity, as demonstrated for RanGTP, a small guanosine triphosphatase involved in spindle assembly (*32*), perhaps counteracted in the cytoplasm by other molecules. Our data and that of other groups also point to a role for centrioles in regulating total centriole number, because their presence precludes de novo formation (Fig. 1D and fig. S11) (*5*, *6*). This is true even in a large embryo (~800 μm) containing very large amounts of SAK (Fig. 1D). Whether this indicates sequestering of active SAK or its substrates in existing centriolar structures or an active inhibitory effect of centrioles upon de novo assembly requires further study.

The regulation of SAK activity is essential in the control of centriole number (fig. S11) and may be a parameter that is regulated according to cellular needs, because multiciliated cells of the respiratory tract have high SAK levels (*19*). The activity of SAK may be inhibited in the acentriolar female meiosis, as de novo centrosome formation only occurs after meiosis exit in eggs overexpressing SAK (Fig. 2). *Drosophila* eggs and embryos should provide an ideal experimental system for further analyses of the control of centriole biogenesis and how it may go awry in cancer.

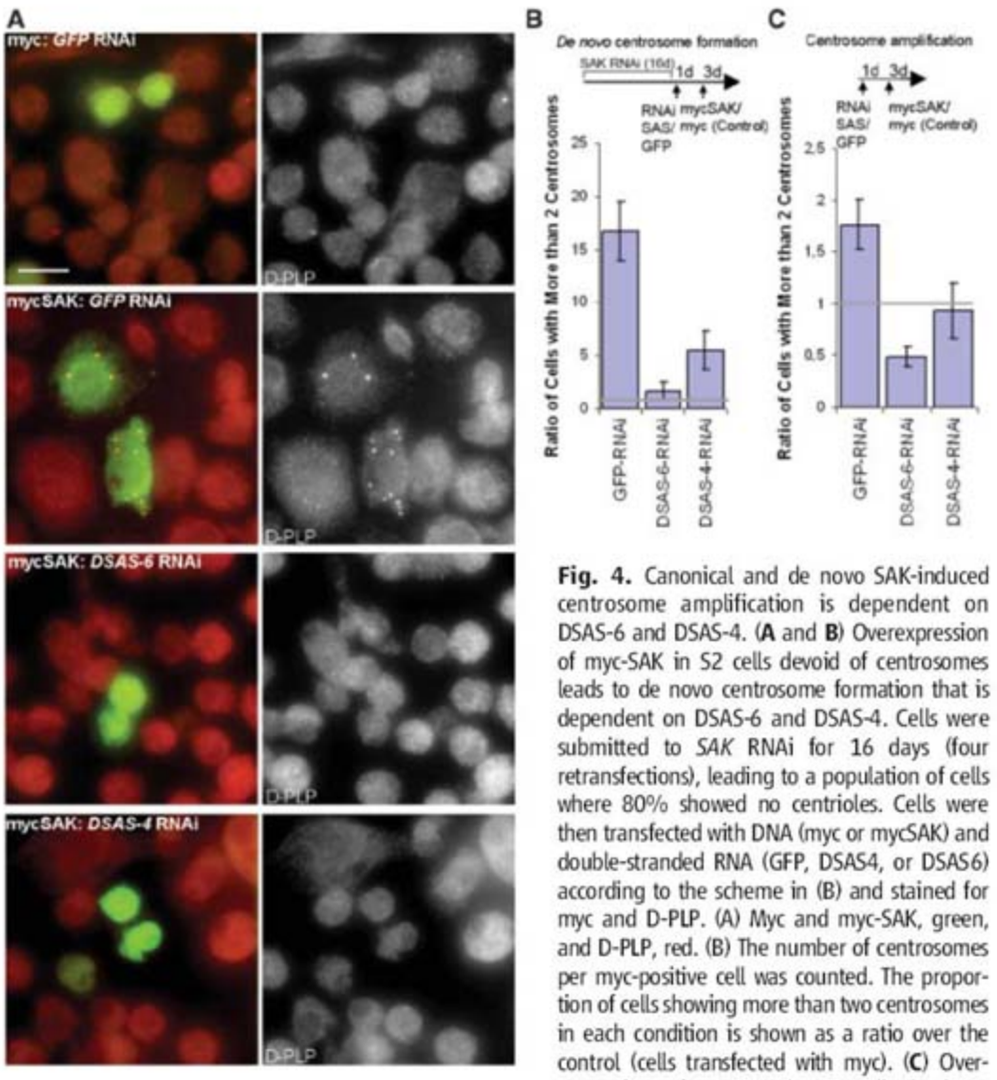

Fig. 4. Canonical and de novo SAK-induced centrosome amplification is dependent on DSAS-6 and DSAS-4. (**A** and **B**) Overexpression of myc-SAK in S2 cells devoid of centrosomes leads to de novo centrosome formation that is dependent on DSAS-6 and DSAS-4. Cells were submitted to *SAK* RNAi for 16 days (four retransfections), leading to a population of cells where 80% showed no centrioles. Cells were then transfected with DNA (myc or mycSAK) and double-stranded RNA (GFP, DSAS4, or DSAS6) according to the scheme in (B) and stained for myc and D-PLP. (A) Myc and myc-SAK, green, and D-PLP, red. (B) The number of centrosomes per myc-positive cell was counted. The proportion of cells showing more than two centrosomes in each condition is shown as a ratio over the control (cells transfected with myc). (**C**) Overexpression of mycSAK in S2 cells leads to centrosome amplification that is dependent on DSAS-6 and DSAS-4. The same experiment as in (B) was performed, but this time in a population of cells not submitted previously to SAK RNAi. Scale bar, 10 μm. A minimum of 100 cells were counted for each condition in each of three independent experiments. Error bars indicate standard deviation.

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Combined Action of PHD and Chromo Domains Directs the Rpd3S HDAC to Transcribed Chromatin

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Nucleosomes must be deacetylated behind elongating RNA polymerase II to prevent cryptic initiation of transcription within the coding region. RNA polymerase II signals for deacetylation through the methylation of histone H3 lysine 36 (H3K36), which provides the recruitment signal for the Rpd3S histone deacetylase complex (HDAC). The recognition of methyl H3K36 by Rpd3S requires the chromodomain of its Eaf3 subunit. Paradoxically, Eaf3 is also a subunit of the NuA4 acetyltransferase complex, yet NuA4 does not recognize methyl H3K36 nucleosomes. In *Saccharomyces cerevisiae*, we found that methyl H3K36 nucleosome recognition by Rpd3S also requires the plant homeobox domain (PHD) of its Rco1 subunit. Thus, the coupled chromo and PHD domains of Rpd3S specify recognition of the methyl H3K36 mark, demonstrating the first combinatorial domain requirement within a protein complex to read a specific histone code.

Histone modifications are important for almost all DNA-related processes, but studies of the role of histone methylation in transcription regulation have become a major focus in the field (*1*). Methylated lysines K4me, K36me, and K79me are enriched around regions of active transcription (*2*, *3*). These methylation marks do not simply facilitate transcription, because K4me does not affect transcription per se in vitro (*4*). Moreover, for the majority of the yeast genome, transcription occurs normally in the absence of K4me, K36me, or K79me, whereas methylation appears to be dependent on active transcription (*5*). These observations imply that methylation acts in maintaining the architecture of transcribed-chromatin templates, rather than directly facilitating transcription. Consistent with this hypothesis, recent studies demonstrate that K36me is recognized by the chromodomain of its Eaf3 subunit (CHD_{Eaf3}) within Rpd3S, thereby tethering Rpd3S to the coding region of actively transcribed genes. Once targeted, Rpd3S creates a hypoacetylated state, which in turn suppresses transcription initiated within the body of the gene (*6*–*8*).

Many chromatin-related complexes contain multiple domains that can recognize specific histone marks, but their contributions to the specificity and function of the complexes remain elusive. We discovered a critical role of the plant homeobox domain of the Rco1 subunit (PHD_{Rco1}) in Rpd3S targeting. Our data suggest that CHD_{Eaf3} and PHD_{Rco1} contribute combinatorially to the overall affinity and specificity of Rpd3S for its nucleosomal targets, and both domains are essential for Rpd3S-mediated control of global-acetylation levels at transcribed chromatin in vivo.

Previous studies have demonstrated that the CHD_{Eaf3} in Rpd3S preferentially binds to K36me2 histone peptides (*6*, *7*). We wanted to further test Rpd3S binding in a nucleosomal context. To measure the binding of Rpd3S to modified nucleosomes, we developed an assay. Reconstituted recombinant nucleosomes were immobilized on magnetic beads, sequentially modified, and then washed to remove the modifying enzymes. The resulting nucleosomes were released by restriction digestion, as illustrated in Fig. 1A. We examined the following combinations of modifications: mock-modified, acetylated by Spt-Ada-Gcn5-acetyltransferase and NuA4, methylated at H3K36 by the recombinant hSet2 (Fig. 1, B and C), and both acetylated and methylated. We found that Rpd3S bound to methylated nucleosomes with a higher affinity than to either unmodified or acetylated nucleosomes, and acetylation further enhanced the binding of Rpd3S to the methylated nucleosomes (Fig. 1D). However, Rpd3S was unable to bind the 147–base pair nucleosome lacking linker DNA, even when the appropriate modifications were present (Fig. 1E). The recognition of K36me by Rpd3S is specific because H3K79me does not stimulate Rpd3S nucleosomal binding (fig. S3).

CHD_{Eaf3} plays a pivotal role in recruiting Rpd3S to chromatin, both in vitro and in vivo (*6*–*8*). We constructed a mutant Rpd3S complex in which CHD_{Eaf3} was deleted (*eaf3*Δchd). The wild-type (WT) and mutant complexes were purified by tandem affinity purification (TAP)–tagged Rco1. Based on silver-stained gels, the deletion of CHD_{Eaf3} did not affect the integrity of Rpd3S (Fig. 2A). This deletion did, however, substantially reduce the affinity of Rpd3S for nucleosomes (Fig. 2B), as only weak binding of the mutant

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Rpd3S was detected at concentrations 12 to 24 times that of the WT complex. More importantly, the mutant complex no longer discriminated between methylated and unmethylated nucleosomes. These data indicated that CHD_{Eaf3} not only contributes to the overall affinity of Rpd3S for nucleosomes, but also determines the specificity of Rpd3S binding to K36-methylated nucleosomes.

Eaf3 is also a component of the NuA4 histone acetyltransferase complex. We wished to find out if CHD_{Eaf3} was important in the binding of NuA4 to nucleosomes, in a manner similar to its role in Rpd3S. When purified, NuA4 (Epl1-TAP) and Rpd3S (Rco1-TAP) were directly compared by electrophoretic mobility shift assay (EMSA); NuA4 did not associate with nucleosomes under conditions where Rpd3S bound (Fig. 3A). These data suggest that the Eaf3 subunit, in the context of NuA4, does not support stable binding to nucleosomal substrates.

We considered the possibility that Eaf3 might work cooperatively with another subunit of Rpd3S to enhance its specificity for K36me. PHD_{Rco1} represents a potential chromatin-binding domain within the Rpd3S complex. The association of Rco1 with Rpd3S is mutually dependent on Eaf3, making both proteins essential for Rpd3S function (*6*). To evaluate the role of PHD_{Rco1} in Rpd3S function, we tested whether the mutant bearing a deletion of the PHD domain alone (*rco1*Δphd) caused a phenotype similar to that of deletion of the entire Rpd3S complex. We employed two different approaches to address this question.

Earlier studies demonstrated that defects in the Set2-Rpd3S pathway led to hyper-acetylation of coding regions at selected yeast genes (*6*–*8*). To determine whether this observation applied genomewide, we performed chromatin immunoprecipitation coupled with microarrays (ChIP-chip) experiments on a high-density tiling microarray platform with the use of an antibody against acetylated histone H4 (AcH4). The enrichment of AcH4 in *set2*Δ and the wild type was directly compared, and the resulting log 2 ratios were subjected to a modified average-gene analysis (*3*). This analysis allowed us to evaluate the average distribution profile of acetylation changes genomewide. The resulting profile revealed a peak within the 3′ portion of coding regions across the entire genome (Fig. 3B). Remarkably, using a similar ChIP-chip approach, we found that removal of either *eaf3*Δchd or *rco1*Δphd resulted in global-acetylation changes similar to those seen in *set2*Δ (Fig. 3B). Therefore, CHD_{Eaf3} and PHD_{Rco1} were essential for Rpd3S to regulate global acetylation at open reading frames (ORFs). Second, defects in the Set2-Rpd3S pathway result in the generation of aberrant internally initiated transcripts at the *STE11* locus (*6*). Thus, we

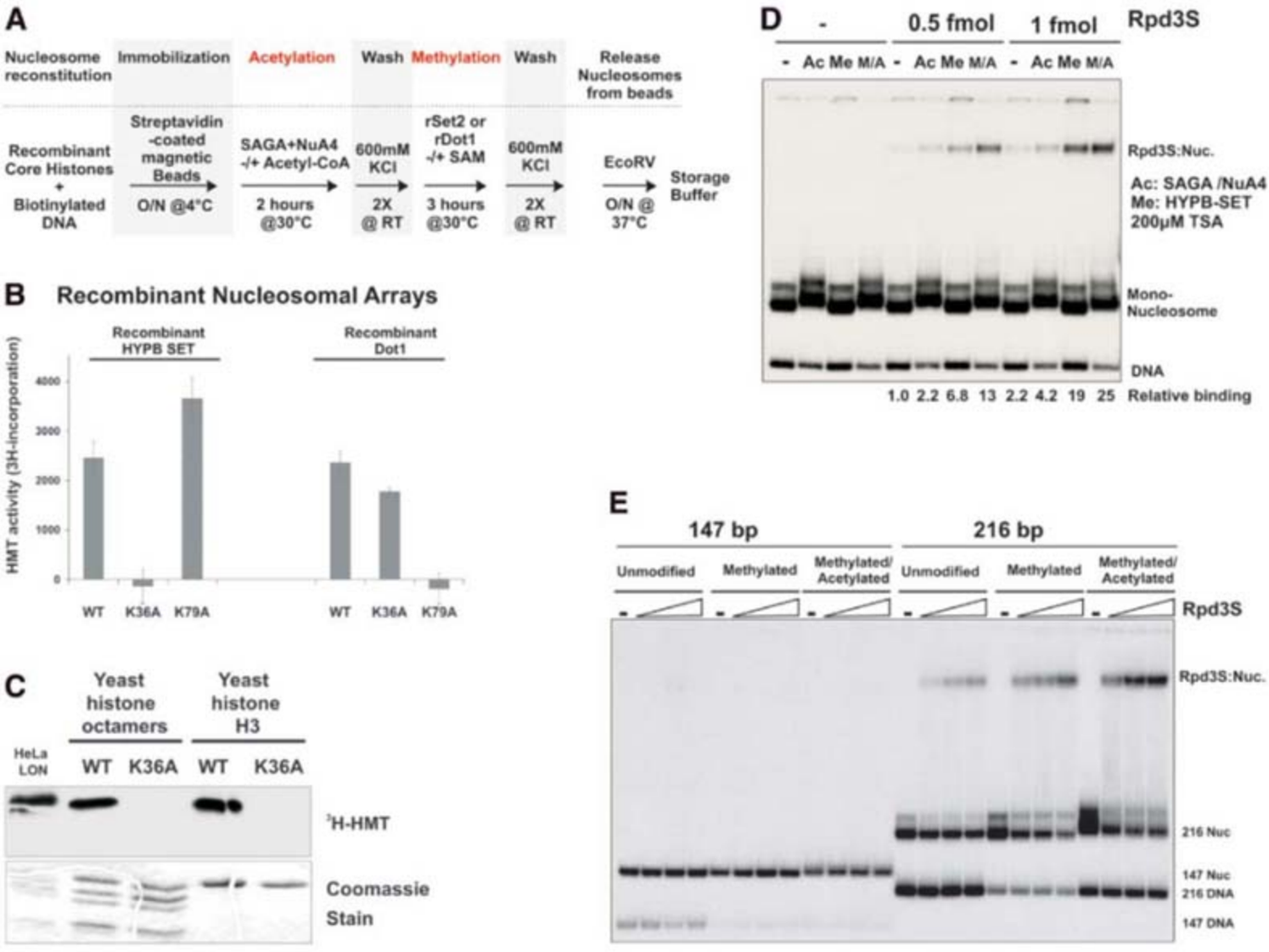

Fig. 1. Rpd3S preferentially binds to nucleosomes methylated at K36. (**A**) Outline of the experimental strategy, using immobilized templates to make covalently modified nucleosomes. O/N, overnight; CoA, coenzyme A; RT, room temperature; SAM, *S*-adenosylmethionine. (**B** and **C**) hSet2 and rDot1 specifically methylate recombinant nucleosomes at the desired sites. Error bars in (B) indicate SD. HMT, histone methyltransferase; HYPB SET, the SET domain of HYPB; LON, long oligo-nucleosomes. (**D**) Rpd3S preferentially binds to K36-methylated nucleosomes, and acetylation further enhances its association. -, unmodified; Ac, acetylated; Me, methylated; M/A, methylated and acetylated; TSA, trichostatin A. (**E**) The linker DNA is required for Rpd3S binding to the hyper-methylated and hyperacetylated nucleosomes.

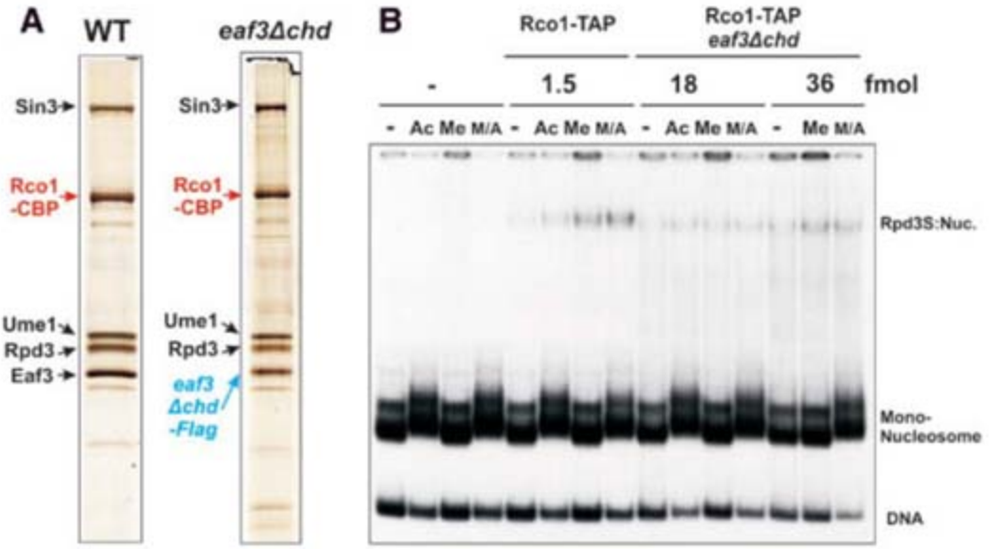

Fig. 2. CHD_{Eaf3} is important for Rpd3S nucleosome-binding specificity. (**A**) Deletion of CHD_{Eaf3} does not affect the integrity of the Rpd3S complex. The WT (left) and *eaf3*Δchd (right) forms of the Rpd3S complex were purified through the Rco1-TAP tag and visualized by silver staining. CBP, calmodulin binding protein. (**B**) Deletion of the chromodomain reduces overall affinity of Rpd3S for nucleosomes and abolishes its specificity toward K36-methylated nucleosomes.

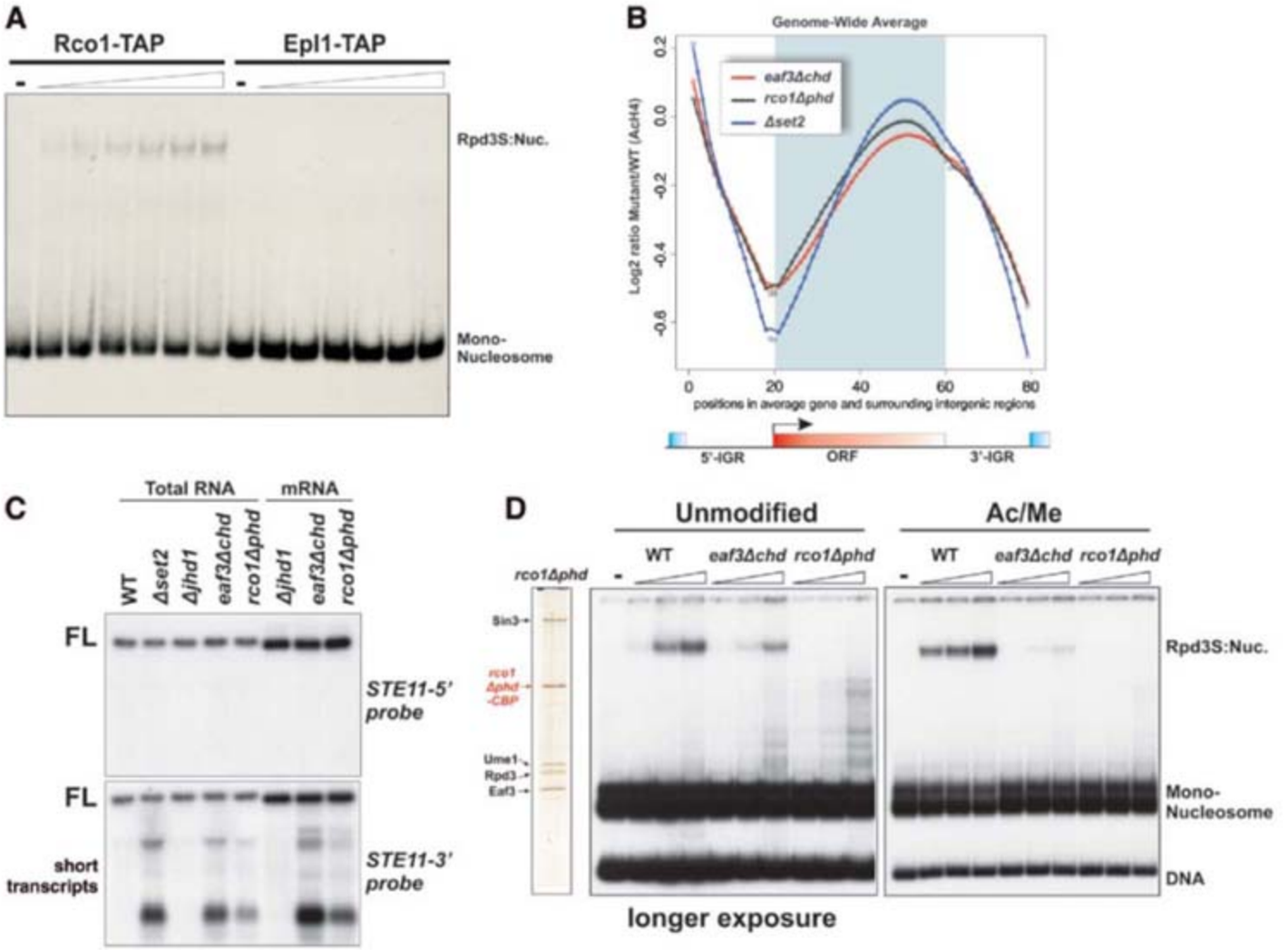

Fig. 3. The PHD domain of Rco1 is required for normal function of Rpd3S. (**A**) Eaf3 plays different roles in NuA4 and Rpd3S. (**B**) PHD_{Rco1} and CHD_{Eaf3} are essential for regulating global acetylation at ORFs. WT yeast and strains bearing *eaf3*Δchd (YBL619), *rco1*Δphd (YBL632), or *set2*Δ mutations were subjected to ChIP-chip analysis on a high-resolution tiling microarray platform (Agilent Technologies, Santa Clara, CA) with the use of AcH4. The enrichment values were first calculated using the log 2 ratio of immunoprecipitated (IP) versus input. Subsequently, the log 2 ratio for the enrichment of acetylation of H4 (AcH4) in the mutant versus the enrichment of AcH4 in the wild type were pipelined into a modified average-gene analysis (*3*). The averages of the entire genome are plotted against the relative position of the 5′ intergenic region (IGR), ORF, and 3′ IGR in an average gene. The line in the graph was created by using the *R* function lowess to smooth the average values. (**C**) PHD_{Rco1} is required for suppression of spurious transcription. Northern blot analysis of yeast strains grown exponentially was performed using probes against *STE11*. FL, full length. (**D**) PHD_{Rco1} is required for Rpd3 nucleosome binding. Silver staining of the mutant Rpd3S complex (*rco1*Δphd) is shown (left). The amount of complex used here was normalized, based on silver staining and Western blot with an antibody to CBP (fig. S7).

performed Northern blot analysis with probes against the 5′ and 3′ portion of *STE11*. Deletion of PHD_{Rco1} resulted in the appearance of spurious transcripts, similar to those seen in *set2*Δ (Fig. 3C). Collectively, these results suggest that PHD_{Rco1} is required for Rpd3S function in vivo.

To further dissect the molecular function of PHD_{Rco1} in Rpd3S, we purified the *rco1*Δ*phd* mutant Rpd3S complex. Although the deletion of PHD_{Rco1} does not disrupt the integrity of the complex, based on silver-stained SDS–polyacrylamide gel electrophoresis (PAGE) (Fig. 3D, left), it completely abrogates the binding of Rpd3S to nucleosomes (Fig. 3D). This result indicates that one essential role for PHD_{Rco1} is to enhance the overall affinity of Rpd3S for nucleosomes, whereas CHD_{Eaf3} provides specificity for H3K36-methylated nucleosomes.

The inhibitor-of-growth (ING) family of proteins contains PHD domains (PHD_{ING}) that preferentially bind to H3K4me3 (*9*). We found that PHD_{Rco1} is structurally different from PHD_{ING}, and it does not recognize methylated H3K4me (fig. S10). Because functional Rpd3S requires both PHD_{Rco1} and CHD_{Eaf3}, we hypothesized that Rpd3S nucleosome-binding affinity might be dictated by the combined activities of these two domains. NuA4 contained CHD_{Eaf3} but paired with a structurally different PHD_{Yng2}. This combination might not be suitable for persistent chromatin binding. To test this theory, we performed an experiment in which PHD domains of Yng2 and Rco1 were swapped (Fig. 4).

First, PHD_{Rco1} was replaced by PHD_{Yng2} at the genomic locus, and this mutant Rpd3S was purified though a TAP-tagged Rco1. Although the chimeric Rco1 was stably incorporated into Rpd3S (Fig. 4A, left), the mutant complex was not able to bind nucleosomes (Fig. 4A, right), similar to the *rco1*Δphd mutant (Fig. 3D). This result suggests that the combination of PHD_{Yng2} and CHD_{Eaf3} does not direct nucleosome binding, even in the context of Rpd3S.

Next, we purified mutant NuA4 complexes in which PHD_{Yng2} was replaced by PHD_{Rco1} at the genomic locus. The fusion Yng2 was stably incorporated into NuA4 and did not change the stability of the complex (Fig. 4B, left). The Yng2-$Rco1_{PHD}$ protein increased the overall affinity of the NuA4 complex for nucleosomes (Fig. 4B, right). This increase in binding was considered notable, because the unbound fraction of nucleosomes was clearly reduced after the addition of Yng2-$Rco1_{PHD}$–containing NuA4. Using a ChIP assay, we further demonstrated that this altered form of NuA4 is redirected to the coding region of *STE11* (Fig. 4C). More importantly, this mistargeting of the mutant NuA4 onto the ORF results in the appearance of cryptic transcripts, even in the presence of WT Rpd3S (Fig. 4D,

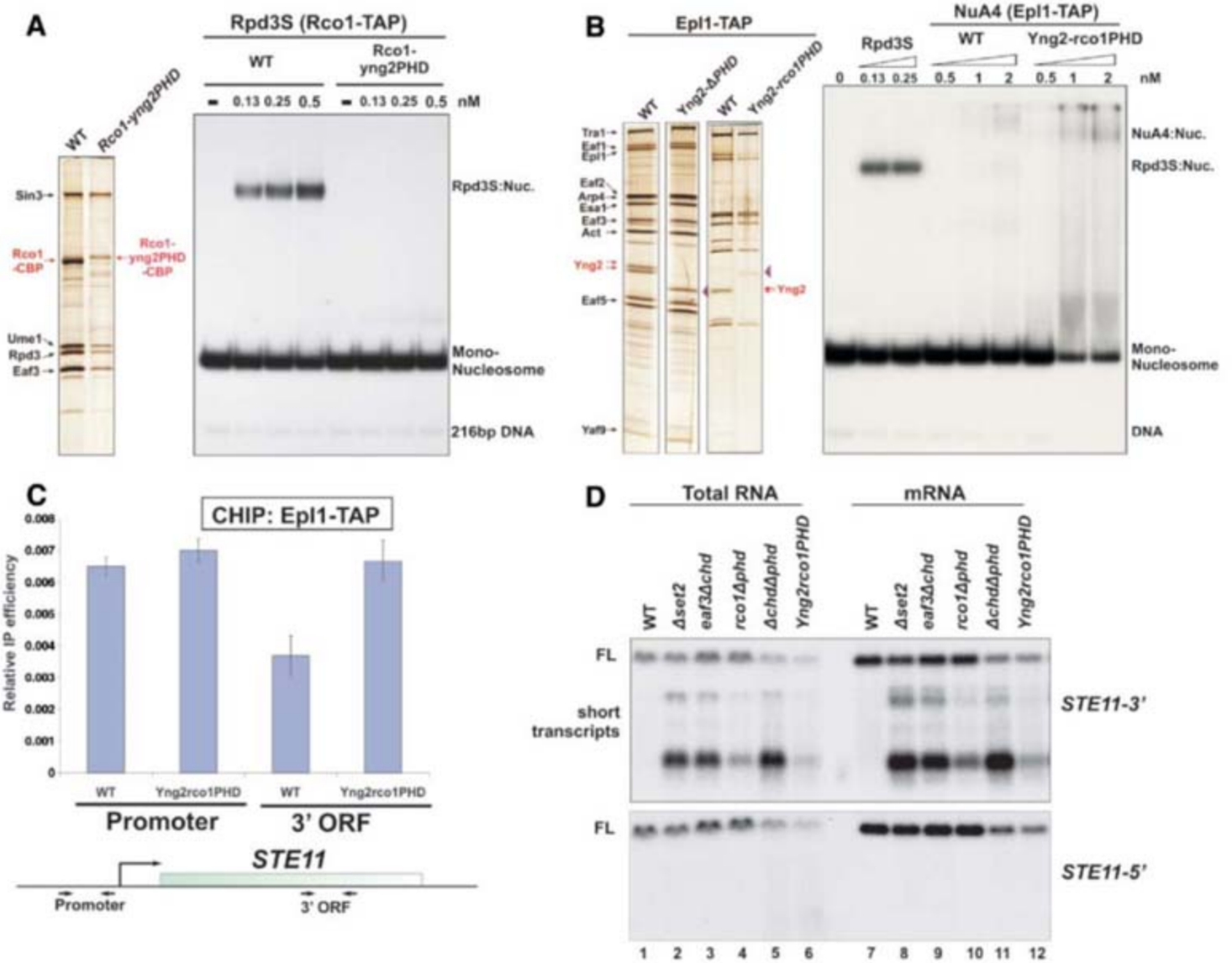

Fig. 4. Specific domain combinations determine the nucleosomal binding of chromatin modifying complexes. (**A** and **B**) Silver staining of WT and indicated mutant complexes (left). EMSA (right). Red arrowheads in (B) indicate mutant Yng2. (**C**) Cross-linked extracts from the wild type and Yng2-rco1PHD (YBL677) were immunoprecipitated with rabbit–immunoglobulin G (Epl1-TAP). Purified DNA was quantified using real-time polymerase chain reaction with the indicated primer sets. Error bars indicate SD. (**D**) RNA from Δchd Δphd (YBL694) and Yng2rco1PHD (YBL677) were included in the Northern blot analysis using *STE11* probes.

lanes 6 and 12). These results strongly support the notion that combinatory actions of CHD_{Eaf3} and PHD_{Rco1} determine the targeting of the chromatin-related complexes to H3K36me-enriched regions

Since the histone-code hypothesis was proposed (*10*), many domains within chromatin-related complexes have been discovered that recognize specific histone modifications. Complexes with different (sometimes even opposite) functions contain identical domains within shared subunits (*5*). Given this apparent overlap in domain usage, cells must have a system to ensure that the correct complex is recruited to specifically modified nucleosomes. Our study suggests that the combination of multiple domains within a chromatin-related complex is important for interpretation of the histone code. In Rpd3S, PHD_{Rco1} does not bind to naked DNA (data not shown in the figures) nor to the histone K4me mark (fig. S10), yet it is required for robust nucleosome binding. As for CHD_{Eaf3}, it is essential for recognition of the K36-methylation mark (Fig. 2B) (*6*–*8*). Moreover, CHD_{Eaf3} contributes to the overall affinity of the complex for nucleosomes because a higher concentration of the mutant *eaf3*Δchd complex is required to achieve basal binding. Thus, the binding of PHD_{Rco1} to nucleosomes may anchor Rpd3S in a configuration that allows CHD_{Eaf3} to recognize K36me. Without PHD_{Rco1}, CHD_{Eaf3} might not be positioned properly or have enough affinity, thereby failing to support nucleosome binding (Fig. 3D). The deletion of both domains affects the integrity of Rpd3S and results in a stronger spurious-transcription phenotype (Fig. 4D and fig. S9). Furthermore, the substitution of PHD_{Yng2} with PHD_{Rco1} can increase the affinity of NuA4 for nucleosomes both in vitro and in vivo (Fig. 4). This result strongly suggests that the specific combination of CHD_{Eaf3} and PHD_{Rco1} in the context of either Rpd3S or NuA4 directs robust nucleosome binding. Therefore, our study presents a mechanism for substrate recognition by a chromatin-related complex. Future studies into how combinations of recognition domains affect the complexity of these enzymes under different physiological conditions are of great interest.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/316/5827/1050/DC1
Materials and Methods
Figs. S1 to S11
Tables S1 and S2
References

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Conformational Switching in the Fungal Light Sensor Vivid

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The *Neurospora crassa* photoreceptor Vivid tunes blue-light responses and modulates gating of the circadian clock. Crystal structures of dark-state and light-state Vivid reveal a light, oxygen, or voltage Per-Arnt-Sim domain with an unusual N-terminal cap region and a loop insertion that accommodates the flavin cofactor. Photoinduced formation of a cystein-flavin adduct drives flavin protonation to induce an N-terminal conformational change. A cysteine-to-serine substitution remote from the flavin adenine dinucleotide binding site decouples conformational switching from the flavin photocycle and prevents Vivid from sending signals in *Neurospora*. Key elements of this activation mechanism are conserved by other photosensors such as White Collar-1, ZEITLUPE, ENVOY, and flavin-binding, kelch repeat, F-BOX 1 (FKF1).

The PAS (Per-Arnt-Sim) protein superfamily transduces signals from diverse biological cues, often by coupling cofactor chemistry to alterations in protein conformation or association (*1*). The canonical PAS domain protein photoactive yellow protein (PYP) and the light, oxygen, or voltage (LOV) PAS subclass sense blue light in bacteria, plants, and fungi (*2*, *3*). Despite extensive photochemical and structural characterization of such blue-light sensors (*2*, *4*–*8*), the mechanism by which cofactor excitation leads to biological signal propagation remains an open question.

The filamentous fungus *Neurospora crassa* employs two blue-light sensors with LOV domains, White Collar-1 (WC-1) and Vivid (VVD) to regulate a variety of light responses (*9*). WC-1 and nonphotosensitive WC-2 form a complex (WCC) that resets the circadian clock by activating transcription of the clock oscillator protein Frequency (FRQ), as well as many other genes (*9*, *10*). VVD, a small PAS protein devoid of auxiliary domains, tunes *Neurospora*'s blue-light response by attenuating activation of the WCC. VVD is essential for response to changing levels of light and for adaptation under constant light (*11*–*14*). VVD and WC-1 share sequence similarity in a core LOV domain and surrounding regions (*15*). Swapping the WC-1 core LOV domain with that from VVD maintains some light responses in *Neurospora* (*16*). VVD and WC-1 require flavin adenine dinucleotide (FAD) for activity instead of flavin mononucleotide (FMN), which is used by plant and algal LOV-containing proteins known as phototropins (*9*, *12*, *17*, *18*).

We report the crystal structure of VVD in its dark- and light-adapted states and show how chemical changes at the active center generate conformational change at the N terminus of the protein. We also characterize a Cys-to-Ser residue substitution outside of the canonical LOV domain that decouples the photocycle from conformational switching. *Neurospora* harboring this mutation lose adaptive light responses, such as the ability to down-regulate carotenoid biosynthesis.

A 36-residue N-terminal truncation of VVD contains the region homologous to the LOV domain of WC-1 and maintains the photochemical properties of the wild type (WT) (Fig. 1) (*12*); moreover, the shortened protein has dramatically increased solubility and stability at room temperature. The 2.0 Å resolution structure of VVD-36 (table S1) reveals a typical PAS domain topology for the protein core (*3*) (Fig. 1A and fig. S1). Similar to the phototropins, the flavin isoalloxazine ring binds in a pocket formed by helices Eα and Fα and the three strands of the central β sheet (Aβ, Hβ, and Iβ) (*4*, *19*) (Fig. 1A). Despite these similarities, VVD contains two structural components that distinguish it from phototropin-like LOV domains.

First, an 11-residue inserted loop between Eα and the helical connector (Fα) accommodates the adenosine moiety of FAD at the surface of the protein (Fig. 1A). The blue-light using FAD (BLUF) family of FAD-containing light sensors also places the adenosine in a solvent-exposed environment, where it has been proposed to mediate protein/protein interactions (*20*). Nevertheless, in full-length VVD, residues 1 to 36 (absent in VVD-36) may sequester the adenosine moiety in the dark state. Second, an N-terminal cap (res-

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idues 37 to 70) that includes helix aα and strand bβ differs in structure from analogous regions of known PAS proteins (Fig. 1, A and B). In two different crystal forms, VVD associates as a symmetric dimer via a hydrophobic face of aα (Fig. 1A). However, in solution, VVD is monomeric for both dark- and light-adapted states. The N-terminal cap in VVD-36 resides at a similar position against the canonical β sheet as the N-terminal cap in PYP (*3*), the C-terminal Jα-helix in the *Avena sativa* LOV2 domain (AsLOV2 phototropin) (*5*), and the αF helix in the *Drosophila* clock protein Period (*21*), all of which have been implicated in conformational switching (Fig. 1B). To date, no definitive evidence has linked conformational changes in these regions to in vivo biological function.

Upon blue-light excitation, VVD undergoes a photocycle similar to that of the LOV domains from phototropins (*7*, *12*). Excitation of the oxidized flavin ring promotes formation of a covalent adduct between a Cys thiol and the flavin C4a position (Fig. 1C). Attack of the thiol at C4a reduces the flavin ring, breaks aromaticity, and bleaches the absorption bands at 450 and 478 nm (Fig. 1C and fig. S2). Scission of the thioether bond and return to the dark state at room temperature is much slower ($t_{1/2}$ = 1 × 10^4 s) than seen in phototropins ($t_{1/2}$ = ~200 s) (*22*), but similar to the recovery of the LOV-containing protein YTvA (~3 × 10^3 s) (*23*) (Fig. 1C). In VVD, conserved Cys^{108} is directly above the C4a position in the dark-state structure, but the residues surrounding the flavin ring differ considerably from those found in structurally characterized phototropins (Fig. 2A) (*2*, *12*). Similar to that observed in an algal LOV1 domain (*4*), an alternative, minority conformation is found for the active center Cys. In VVD, this minority conformer places the Cys^{108} thiol within 3.4 Å of conserved Cys^{76}, which is at the end of a water channel leading to the flavin (Fig. 2A). The two Cys residues are close enough for disulfide bond formation; however, substantial adjustments would be necessary to obtain optimum disulfide geometry. Oxidation or modification at either Cys could inhibit VVD from forming the light-state adduct and provide a means for regulation of VVD activity by reactive oxygen species (*24*).

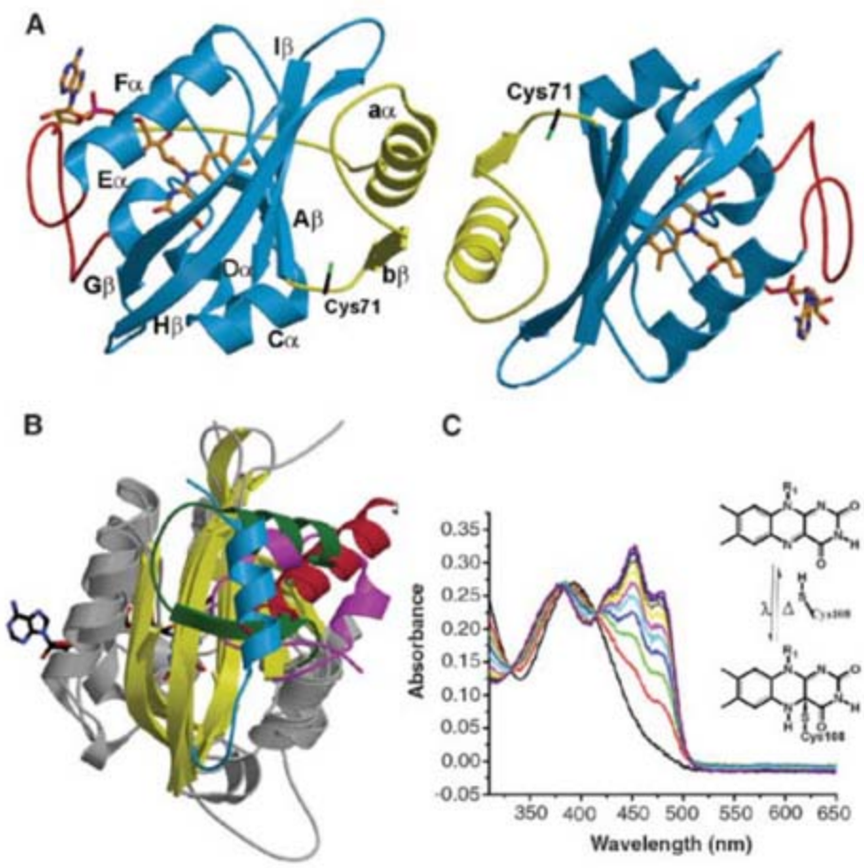

Fig. 1. VVD structure. (**A**) Crystallographic dimer of VVD-36, including the PAS core (blue), N-terminal cap (yellow), and FAD insertion loop (red). The N terminus, resolved only in the left molecule, projects toward the solvent-exposed FAD adenosine moiety (orange). (**B**) Superposition of the PAS domains of VVD (green), PYP (magenta), *Drosophila* PER (red), and AsLOV2 domain (blue). All proteins share a structurally conserved PAS β scaffold (yellow) and helical regions (gray) that pack with a variable helical element possibly involved in signal transduction. (**C**) Photocycle of VVD-36 at 25°C. Blue-light illumination of VVD forms a photoadduct between Cys^{108} and the C4a position of the flavin ring (inset). Adduct formation bleaches the flavin absorption bands at 428, 450, and 478 nm and produces a single peak at 390 nm. Recovery proceeds with $t_{1/2}$ = 10^4 s and three isosbestic points at 330, 385, and 413 nm. Spectra are displayed at 3000 s increments.

To probe conformational changes in the flavin adduct state of VVD-36, structures were determined for photo-bleached crystals (table S1). A high-occupancy/high resolution (1.7 Å) light-state structure was determined by combining the first 30 frames of diffraction data from four different crystals that were exposed to light before rapid cooling in liquid N_2. Exposure to the synchrotron beam reduces the VVD flavin and breaks the C4a adduct; thus, only minimally exposed crystals contain a significant fraction (~50%) of the covalently coupled cofactor. Difference Fourier electron-density maps ($F_{observed} - F_{calculated}$) (Fig. 2B and fig. S3) reveal clear bonding of Cys^{108} to flavin C4a and conformational changes at Gln^{182}, which hydrogen-bonds with flavin N5. Thioether bond formation reduces the flavin ring and protonates N5. To maintain a hydrogen bond with protonated N5, the amide of Gln^{182} must flip (*4*, *25*, *26*). The VVD structure at 1.7 Å resolution shows clear difference density for flipping of the Gln^{182} amide (Fig. 2B). Moreover, these altered interactions of Gln^{182} subtly affect the conformation of a hinge region connecting the N-terminal cap to the PAS core. In the dark state, the side-chain carbonyl of Gln^{182} abuts the carbonyl carbon of Ala^{72} (Fig. 2, C and D). In the light state, the Gln^{182} flip replaces this potentially unfavorable contact with a hydrogen bond between the Ala^{72} carbonyl and the Gln^{182} amide nitrogen. The Gln^{182} flip alters dipole orientations and perhaps stabilizes Ala^{72} against bβ (Fig. 2, C and D). The Cys^{71} thiol breaks a buried hydrogen bond to the Asp^{68} carbonyl and rotates into a more exposed position to interact with the Asp^{68} peptide nitrogen (Fig. 2D and fig. S4). The altered interactions of Cys^{71} correlate with a shift in bβ of 2.0 Å toward the PAS core (Fig. 2, C and D). The translation of bβ disrupts interactions made by Met^{55} and Arg^{57} that otherwise stabilize packing of the N-terminal cap against the PAS β sheet (Fig. 2C). No other major structural changes are observed in the crystalline protein on photoexcitation. For example, there were no perturbations to a salt bridge between Asp^{82} and Arg^{109} that has been suggested to mediate conformational changes within the phototropins and YtvA (*6*, *25*, *27*).

Although structural changes in the bleached crystal are modest, VVD-36 undergoes a large change in hydrodynamic radius on solution excitation that is readily apparent on a sizing column because of slow recovery of the light state (Fig. 3A and table S2). This shift in elution volume is less pronounced in full-length VVD and smaller than the change that would be caused by dimerization (Fig. 3A). Addition of disordered residues to the N terminus increases the apparent size of both the light and dark states, but removal of N-terminal residues structured in the dark state down-shifts the apparent size of only the light state (Fig. 3A). Thus, the larger hydrodynamic volume for the VVD-36 light state results from increased disorder at the N terminus. Small-angle x-ray scattering (SAXS) measurements confirm that the electron density of VVD-36 is more widely distributed in

the light state than in the dark state but that VVD-36 does not undergo dimerization (fig. S5).

The LOV2 phototropin C-terminal Jα helix and PYP N-terminal helices undergo light-induced dissociations from their respective PAS cores (*5*, *28*, *29*). In contrast, aα in the VVD light-adapted state is unlikely to completely release from the β sheet because mutations made to destabilize aα against the PAS core (e.g., Leu^{51}Glu and Ile^{54}Glu) result in unstable, poorly expressed proteins. Furthermore, the face of aα that is completely exposed in the dark state may make new contacts with the protein core in the light state because some substitutions here (e.g., Ile^{52}Arg) prevent conformational switching. The importance of Gln^{182} for coupling conformational change at the N terminus to the flavin is highlighted by the Gln^{182}Leu mutant, which upon light excitation exhibits normal spectral properties but is defective in switching between the compact and fully expanded conformations (Fig. 4A). Our combined data suggests a model where structural changes in VVD-36 propagate to the N-terminal helix aα, which repacks on the protein surface so as to release the N terminus from the protein core (Fig. 3B).

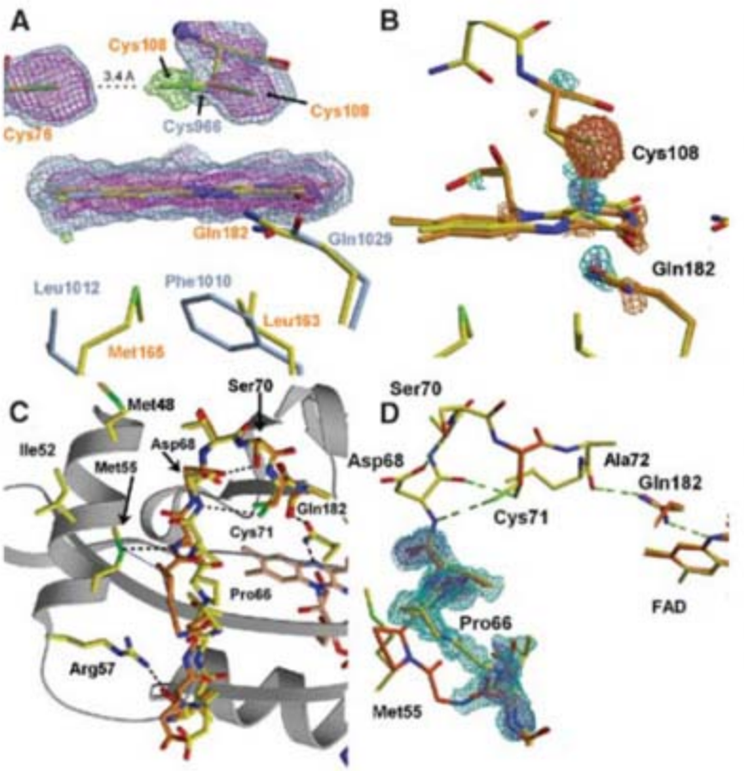

Fig. 2. The VVD light state in crystals. (**A**) Superposition of VVD (yellow) and *Adiantum* phy3-LOV2 (1G28, blue-gray) active centers show differences in residue composition beneath the flavin [1.5 σ (aqua) and 3.0 σ (purple), $2F_{obs} - F_{calc}$ electron density]. An alternate conformation of Cys^{108} contacts conserved Cys^{76} [3.0 σ (green), $F_{obs} - F_{calc}$ electron density]. (**B**) Structural differences in the light state of VVD. Difference electron density reveals covalent bond formation between Cys^{108} and flavin C4a and flipping of the Gln^{182} amide in response to N5 protonation. $F_{obs} - F_{calc}$ electron density [2.0 σ (aqua), 3.0 σ (blue), −2.0 σ (orange), and −3.0 σ (red)], with F_{calc} calculated from a model refined with 100% of the dark-state conformation. (**C**) Expanded view of the structural changes propagating from Gln^{182} to aα and bβ in the VVD-36 light state. Pro^{66} undergoes the largest shift (2.0 Å) in the light state (yellow) versus the dark state (orange). Hydrogen bonds (dashed lines) are shown for $d < 3.2$ Å; except for Cys^{71}-to-Asp^{68} amide, where $d = 3.9$ Å. Other key contacts are shown in blue. (**D**) The hinge region between the PAS core and bβ. In the light state, Gln^{182} rotates to improve interactions between the Gln^{182} amide and the Ala^{72} carbonyl, Cys^{71} swivels to hydrogen-bond with the Asp^{68} amide nitrogen, and bβ shifts 2 Å. $F_{obs} - F_{calc}$ omit electron density [1.5 σ (aqua) and 3.0 σ (purple)] calculated with bβ absent from the model.

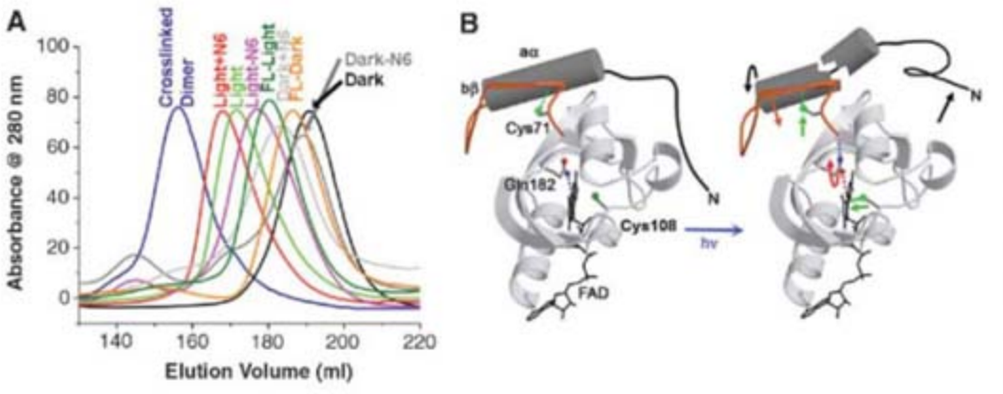

Fig. 3. Increase of the VVD-36 hydrodynamic radius on light excitation. (**A**) Elution profiles of VVD variants from a size-exclusion column. Light-state VVD (green) elutes at a much larger apparent molecular weight than does dark-state VVD (black), but smaller than a disulfide cross-linked dimer (purple). Addition of a His_6 tag to the VVD N terminus shifts the elution profile of both the dark state (light gray) and the light state (red). Truncation of six residues does not affect the dark state (dark gray) but significantly shifts the light state (pink). Full-length VVD undergoes a smaller shift in the light state (dark green) relative to the dark state (orange). (**B**) Model of the coupled chemical and conformational changes caused by VVD light activation.

Mutagenesis experiments designed to probe conformational changes involving the N-terminal cap reveal that substitution of Cys^{71} to Ser completely prevents the N-terminal conformational change (Fig. 4A) but has no other effect on the flavin photocycle ($t_{1/2} = 1 \times 10^4$ s). Cys^{71}, which is conserved in WC-1 and other FAD-binding LOV domains (fig. S1), switches hydrogen-bonding partners upon conversion to the light state (Fig. 2, C and D, and fig. S4). In the 1.8 Å resolution structure of the Cys^{71}Ser mutant, Ser^{71} hydrogen-bonds more closely with the Asp^{68} carbonyl than does Cys^{71} in the WT. Presumably, this buried hydrogen bond stabilizes the loop structure against movement otherwise induced by the altered conformation of Gln^{182}. Substitutions that remove a polar group for hydrogen bonding (Cys^{71}Ala and Cys^{71}Val) recover expansion on light excitation (Fig. 4A). Cys^{71}Ser decouples formation and breakage of the C4a adduct from conformational changes at the N terminus.

Both small and large amplitude conformational changes have been implicated in signal propagation by PAS domain proteins (*2*, *21*, *28*, *30*–*32*); however, it has been challenging to link conformational changes to a biological function in vivo. We performed in vivo complementation studies of VVD Cys^{71}Ser in *Neurospora* to demonstrate that light-induced conformational changes involving the N-terminal cap are essential for cellular function. Introduction of the Cys^{71}Ser mutant into a *vvd* null background demonstrates that the ability of VVD to down-regulate carotenoid production under constant light conditions is completely lost in the decoupled mutant (Fig. 4B). In contrast, a Cys mutant close to the active center, which does not perturb the conformational change (Cys^{76}Ser), behaves as the WT protein when reintroduced to cells (Fig. 4B).

No immediate targets of VVD are known, but its signal must be relayed to the principal photoreceptor of the cell, WC-1. WC-1 likely functions analogously to VVD, because it conserves all of the key structural elements necessary for the VVD conformational switch (fig. S1). When bound to DNA, the WCC migrates with a larger hydrodynamic radius in a gel-shift assay on light excitation (*18*).

Other light sensors, such as WC-1, ENVOY, ZEITLUPE, and FKF-1, have similar residues in

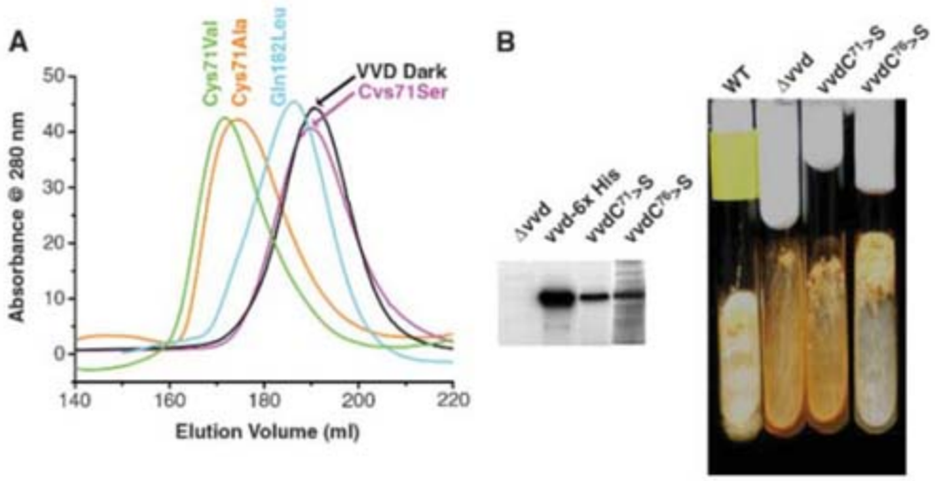

Fig. 4. Decoupling the VVD photocycle from signal transduction. (**A**) Light-state elution profile of VVD-36 variants. A C71A mutant (orange) and C71V mutant (green) adopt the expanded state on light excitation, whereas C71S (pink) cannot. Q182L (aqua) elutes at a position slightly larger than VVD-36 dark (black) but does not respond normally to light excitation. (**B**) VVD C71S is incapable of transmitting blue light signals in *Neurospora*. (Left) Western blots of cellular extracts with an antibody to VVD. The *vvd* null mutant contains no VVD protein, whereas the protein is abundant when complemented with WT VVD containing a 6-His tag, C71S, or C76S. (Right) Slant cultures of *Neurospora crassa* grown under constant light conditions. The *vvd* null and C71S mutants accumulate large amounts of carotenoids as a result of loss of light adaptation, giving the cells an orange color. In contrast, complementation with C76S yields WT behavior.

elements important for VVD's switching mechanism (fig. S1). The VVD Cys^{71} variants demonstrate that some substitutions are tolerated at key positions, such as the equivalent Val found in ENVOY. Interestingly, conformational changes in VVD involve contacts between side chains that are reasonably well conserved (Gln^{182} and Cys^{71}) to the peptide backbone of more variable positions (Ala^{72}, Asp^{68}, and Pro^{66}). FKF1, a distant relative of VVD, contains a Ser at position 71 but also exhibits a deletion of bβ that may compensate by altering the hinge structure. Compared with the core and hinge regions, the N termini within this family are highly divergent, which provides the means to couple with a variety of output signals.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S5
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Behavioral Scientists Get Off the Trail

"If you're in academia and you're applying for a job as a professor, you know exactly what to do," says Eric Gold, a behavioral economist at Fidelity Investments' Center for Applied Behavioral Economics in Boston. But if you are looking for a nonacademic job, "you have to be much more entrepreneurial. … The path isn't already worked out for you."

For many, leaving the well-trodden path can have serious consequences. "Sometimes students come out of a lab feeling so demoralized that they're not following their adviser's path that they can't even take the first step; they think they have nothing to offer," says Diane Witt, program director for behavioral neuroscience and neuroendocrinology at the National Science Foundation in Arlington, Virginia. In fact, she says, they have much to offer. Behavioral scientists' training yields highly marketable skills and knowledge that are valuable to many employers in a wide range of professions.

Here are six examples of behavioral scientists who have stepped off the academic path into some interesting territory. >>

Forecasting health care's future

In 2005, behavioral neuroscientist Lisa Slama was a postdoc in molecular biology at Northwestern University in Evanston, Illinois. She was feeling uncertain about her career path.

"I was studying the regulation of one ion channel on one receptor on one type of neuron in one part of the brain," says Slama, 30. "I wanted to do something that would have a much broader impact." She also wanted to put her writing and oral-presentation skills to work in a corporate environment. As she explored jobs outside academia, she felt hampered by a lack of industry experience, but she wasn't afraid to crash a party. At a job fair intended for undergraduates, Slama connected with Sg2, a company based in Skokie, Illinois, that analyzes emerging clinical developments, technological advancements, and market trends for clients such as hospitals and biotechnology companies.

LISA SLAMA
Ph.D., Neuroscience.
Technology/Market analyst, Sg2

She finished her postdoc, then took a job at Sg2. Now she contributes to the company's neuroscience projects and leads its women's health efforts, studying advances in medical and drug research and technology, health-care developments abroad, demographic projections, and insurance-payment trends that are likely to influence health-care delivery. She consults with clients on a variety of projects: whether to expand a stroke program, for example, or build a neuroscience center, or recruit specialists in a certain area. The aim, she says, is to guide clients' long-term strategic decisions.

"I got lucky," Slama reflects. "I didn't even know there was such a thing as health-care consulting, but I found a job that allows me to use my writing and oral-presentation skills on a daily basis and make an impact on health care in the U.S."

Assembling online communities

Shelly Farnham is a social psychologist and a technophile. Although some fret that our digitally saturated lives separate people, she believes increasingly nimble Web technologies can increase social connectedness, not reduce it. The key, she believes, is filtering the glut of information online, the millions of MySpace profiles, YouTube videos, and Del.icio.us bookmarks.

"Technology provides you with the opportunity to meet thousands more people than you ordinarily would," Farnham says. "But that's not what you want. You want to meet three new people who are the *best* three people. You don't want to just increase access; you want to increase relevance."

SHELLY FARNHAM
Ph.D., Social Psychology.
Social-Networking Software Designer

That's what her business is all about. After finishing her Ph.D. at the University of Washington in 1999, Farnham worked as a researcher in the Social Computing and Community Technologies groups at Microsoft. In 2005, she left Microsoft to found Waggle Labs in Seattle, Washington, with a partner, computer scientist Peter Brown. In addition to consulting for various start-ups, the team designs interactive software: for example, a new social-networking game called RealityAllStarz in which participants challenge one another to complete tasks such as hugging a famous person or making art out of food. Players rate one another's photo-documented efforts and compete for prizes.

Farnham, 37, says her work is much like traditional experimental psychology, in which researchers create interventions to test hypotheses. "You can think of technology as an intervention," she says. "You create it, deploy it, and study its impact." The difference, she says, is that most research is about teasing out details of work that has already been done. "I want to feel like I'm doing something new."

ERIC GOLD
Ph.D., Behavioral Decision Theory.
Economist, Fidelity Investments

Nudging procrastinators

Everyone procrastinates sometimes, and Eric Gold has a pretty good idea why. A behavioral economist with a Ph.D. in behavioral decision theory from Carnegie Mellon University (and master's degrees in psychology, computer science, statistics, and decision-making), Gold is interested in, among other things, inertia: that implacable force that keeps people from filing taxes on time or saving for retirement. Fortunately for him, his interest in how people make decisions—financial decisions especially—is shared by his employer.

CREDITS (TOP TO BOTTOM): MICHELLE BATES; STUART ROGERS PHOTOGRAPHY; PHOTO BY JOHN SOARES

At Fidelity, Gold, 49, conducts research on decision-making and economic behavior and shares his knowledge with other corporate divisions. Fidelity's brokerage company, for example, might ask him to develop Web tools to help customers do financial planning.

"They might come and say, 'We're interested in how our customers are thinking about diversification, to help them understand how their risk tolerance is reflected in their investment decisions. How can we explain this connection?' It's a hard question because it involves how people understand numbers and probabilities. To explain those things, you have to understand what's inside people's heads. Something I'm proud of is that you can look at our Web site and see that it's better because of how we've understood our customers."

Bringing artifacts alive

As a graduate student at Indiana University, Bloomington, anthropologist Elizabeth Babcock decided she wanted to apply her research skills and knowledge to solve tangible problems. So as she wrote her dissertation, she built a portfolio of applied anthropology experiences.

ELIZABETH BABCOCK
Ph.D., Anthropology.
Education and Outreach,
The Field Museum

Now, at 39, Babcock reckons she's in her dream job, developing and evaluating education and outreach programs at the Field Museum in Chicago, Illinois. Her daily tasks run from teaching schoolteachers how to conduct an unforgettable field trip to planning an overnight museum adventure for families. She might spend one day reviewing label text for an Egyptian hieroglyph exhibit and the next accompanying a staff paleontologist on an expedition to a fifth-grade classroom, assembling materials to evaluate whether an exhibit was a success, or meeting with foundation representatives to plan a community-outreach project. Babcock is also in charge of the museum's library collections, which she integrates into education programs.

When she left academic research, Babcock half expected that her days of having scientific colleagues were over. But today, she is surrounded by anthropologists, botanists, geologists, and zoologists. "I have a corps of colleagues here, even though I'm not in an academic department," she says.

Promoting adolescent well-being

Developmental psychologist Jill Denner knew when she was a graduate student at Columbia University that she didn't want a university faculty position. "I wanted my research to have a direct application, and I didn't want to teach," she says. The trouble was, she had no idea how to proceed.

During a postdoc at the University of California, Santa Cruz, she began cold-calling: lots of calls to anyone she could think of who might tell her how she could use her Ph.D. in a real-world setting. One call was to ETR Associates, a California nonprofit focusing on health education and promotion. In 1998, ETR Associates' research department offered her a job.

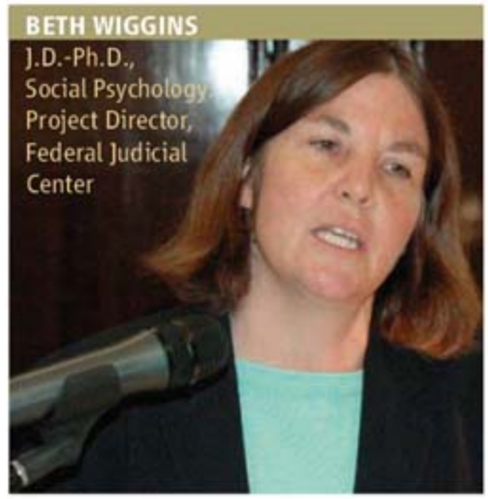
These days, Denner, 39, is a senior research associate at ETR Associates, designing and evaluating programs promoting girls' participation in nontraditional careers, helping to prevent HIV infection and teen pregnancy, and leveraging technology to enhance education.

In one HIV-prevention program, for example, poor, urban high school students role-play difficult social scenarios and do volunteer work in the community. The goal is to learn whether volunteering can boost students' views of themselves and encourage them to take control of their health decisions. In another program, called "Girls Creating Games," Denner studies how computer games can be used to increase the representation of women in the information-technology workforce. "It's amazing to see them realize that they can make a difference in the world," Denner says. "There is so much research knowledge that never makes it out of an academic journal. For me, these programs are just two examples of how psychological research can be put into practice to help youth make positive decisions for themselves and make a contribution to society."

JILL DENNER
Ph.D., Developmental Psychology.
Designer and Evaluator of Social
Programs, ETR Associates

Informing judicial policy

As a project director at the Federal Judicial Center (FJC) in Washington, D.C., the research and education arm of the federal court system, social psychologist Beth Wiggins directs research on topics as varied as the use of technology in courtrooms, the mechanics of dispute resolution, and the consequences of waiving filing fees in consumer bankruptcy court. She develops orientation materials for new federal judges and contributes to continuing education for judges and court staff, work that often incorporates the fruits of her research. As part of FJC's statutory mission to help developing judiciaries elsewhere in the world, she has worked in locales as far-flung as Kosovo and North Africa.



BETH WIGGINS
J.D.-Ph.D.,
Social Psychology
Project Director,
Federal Judicial
Center

"There's a real kick to knowing that somebody is relying on your work," says Wiggins, 49, who has joint J.D.-Ph.D. degrees from Johns Hopkins University in Baltimore, Maryland. "You get addicted to it, in a sense." But the most exhilarating aspect of her work is also the most frightening. "In this environment, when you do a research project, you don't have time to replicate it, and people rely on it to make important decisions. Although it can be frustrating and it carries a lot of responsibility, it challenges us to do the very best we can at the first shot."

Looking back, Wiggins ponders how easy it would have been to *not* take an unconventional path. "Like most graduate students, I was groomed to go into academia," she says. "There was this sense that that's what the 'good' graduate students did. It's so easy in graduate school to be the 'good child,' to do only the things that your adviser or your committee sees as furthering your career." Wiggins recommends a different approach. "Go a little blindly sometimes. Sometimes you'll bomb out, but you'll get there."

–SIRI CARPENTER

Siri Carpenter is a writer in Madison, Wisconsin.

CREDITS (TOP TO BOTTOM): SOURCE: BETH WIGGINS; JOHN WEINSTEIN/THE FIELD MUSEUM 2007; EDWARD JIN

Neuromarketing Careers

Neuromarketing may offer opportunities for Ph.D.s and MBAs able to close the intellectual gap between brain science and market research

Is there a future for you in neuromarketing? Don't count on it just yet, even if you trust the nascent science of using magnetic resonance imaging (MRI) scans to uncover, perhaps even influence, how consumers choose among shampoos, tortilla chips, or hedge funds.

Neuromarketing made a national news splash in 2003, when Read Montague of Baylor College of Medicine in Houston, Texas, used functional MRI (fMRI) technology to explain a famous Coke-Pepsi conundrum: The two sodas are very similar in chemical composition and there's little difference in taste, yet Coke maintains its market dominance. Montague and colleagues found that, both in blind taste tests and in fMRI scans of a brain region associated with taste, subjects were evenly divided in their preference for the two brands. But when Montague's subjects knew they were drinking Coke, brain centers linked to emotion and cognitive control were disproportionately stimulated—which suggested that the powerful cultural wallop of the Coke brand can override the taste buds.


Jordan Knight

Business was intrigued, and it looked at the time as if neuromarketing might become a job engine for Ph.D.s and MBAs able to close the intellectual gap between brain science and market research. Neuroeconomics, the parent discipline that explores links between the brain and economic behavior, seemed poised to make a triumphant leap from academe to Madison Avenue.

A family of psychologists

Four years later, it's still poised. Jordan Knight, a junior at Emory University in Atlanta, Georgia (and also, adventitiously, a champion pole-vaulter on the university's track team), says he's determined to pursue graduate study and a career track in the neuromarketing field. He's a business major but hails from a family of psychologists. His background left him frustrated with his first organization-and-management class at Emory: "I found business professors were dumbfounded to have someone ask about psychology."

Knight responded by enrolling in neuroscience courses and working with Clinton D. Kilts, a psychopharmacologist at Emory School of Medicine's psychiatry department. Kilts, who specializes in addiction studies and bipolar disorder but also maintains an interest in neuromarketing, confirms Knight's experience. "I remember talking to people at the business school," he says, "and being astonished when they'd reach some predetermined conclusion about how decisions are made and then support it by backfilling it with data." Why not use fMRI scans as a way to support or disprove business hunches about how consumers behave? Knight's experience in scoping out graduate programs, however, has persuaded him that the idea hasn't quite taken off. "It's hard to find a program about business and neuroscience; they flat-out don't exist," he says. "The field doesn't really exist yet," Kilts agrees. "We're pasting it together."

PUBLIC OPINION RESEARCH: MEASURING HAPPINESS

The number of jobs in public opinion research is still small, but the field is expanding, and not just in election polling

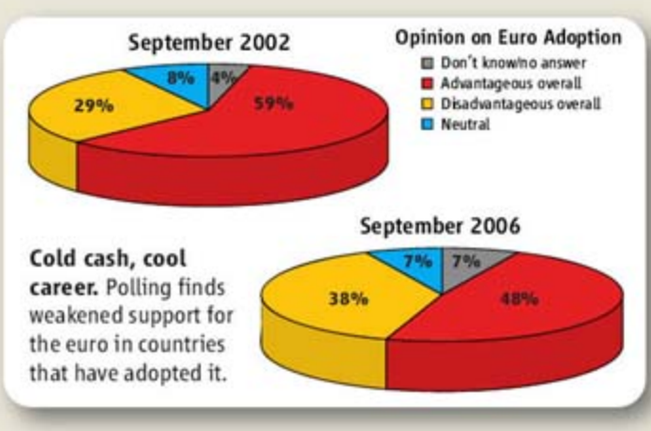
Polls closely tracked the race for the French presidency over the last few weeks, giving candidates and the public an early peek at the likely results. Meanwhile, things are just heating up in the United States, where the elections—and public opinion polling—can be expected to intensify in the next 18 months.

Public opinion research is clearly a thriving business. The number of jobs is still small, but the field is expanding—and not just in election polling. Governments increasingly sample the preferences of their citizens before making policy decisions, media outlets commission polls as part of their reporting, and research organizations map changes in attitudes on social questions.

Surveys tell us, for example, that Ireland embraces the euro, that Danes are happy with their lives, and that people in southern-European countries worry more about climate change than do those at higher latitudes. Researchers in this field attempt to understand cultural attitudes and preferences, then pass that information along to the people who need to hear it. "We give [the public] a voice, in a certain way," says Femke De Keulenaer, a researcher at Gallup Europe in Brussels, Belgium.

Both a career and a science

For behavioral scientists considering a career in public polling research, it helps to have a fascination with numbers. De Keulenaer earned a bachelor's degree in sociology from the University of Ghent in Belgium, and during her master's studies in quantitative analysis at the Catholic University of Brussels, she discovered how numbers "really can explain changes and trends in public opinion" within and across cultures, she says. But it wasn't until her Ph.D. work at the University of Antwerp that she realized that survey methodology "is both a career and a science." Soon after starting her doctoral program, she headed to the University of Nebraska, Lincoln, to train in survey methodology at the Gallup Research Center. The exchange helped her hook up with Gallup Europe, and she joined the organization last year.



Cold cash, cool career. Polling finds weakened support for the euro in countries that have adopted it.


Femke De Keulenaer

CREDITS (CLOCKWISE FROM TOP): JORDAN KNIGHT; FEMKE DE KEULENAER; GRAPHIC SOURCE: FLASH EUROBAROMETER NO. 193, NOV. 2006

Not that there hasn't been progress in research. A recent study at Stanford University in Palo Alto, California, led by Brian Knutson and published in *Neuron*, monitored subjects' brain activity as they shopped online and bought a series of products worth up to $80. Attraction to a product strongly correlated with activity in the nucleus accumbens, which seems to mediate the expectation of pleasure. Too-high prices, on the other hand, stimulated the insula, which anticipates painful stimuli, and quieted the mesial prefrontal cortex, a phenomenon linked to disappointment when a hoped-for reward fails to materialize. MRI readings of these regions predicted whether the subject rejected or bought a product. This is the first time researchers have been able to connect brain activity with a real-life consumer decision.

"This field attracts people who are uninterested in boundaries." —Scott Rick >>

Brian Knutson

Ambivalent about manipulating people

Scott Rick, a co-author of this study and a graduate student in the Social and Decision Sciences Department at Carnegie Mellon University in Pittsburgh, Pennsylvania, was an economics major as an undergraduate. But he revels in neuromarketing's interdisciplinary links between neurophysiology and economics. "This field attracts people who are uninterested in boundaries," Rick says. Yet there is one boundary Rick is not eager to cross: "I'm ambivalent about teaming up with companies to help manipulate people," he says. Instead, he would like an academic career at a business school, but he hasn't found such jobs plentiful. He is choosing at the moment between postdoc offers at the University of Pennsylvania's Wharton School of Business and the California Institute of Technology, which has a cadre of graduate faculty members interested in the field.

George Loewenstein, Rick's adviser, concedes that so far there's really no clear career trajectory for an aspiring neuromarketer. He's not wholly unhappy about that. "If a graduate student in neuroeconomics ended up in industry, that would be a disappointment," Loewenstein says. "The reality is that when you do marketing, you are a slave to economic interests, to people who want to promote certain goods and services."

That gulf in attitudes between academe and Madison Avenue, proverbially wide, still seems to be restraining neuromarketing from making its widely anticipated jump from the laboratory to the marketing department.

–MARK CALDWELL

Mark Caldwell is the author of several books and teaches at Fordham University.

At Gallup Europe, a branch of the 2000-employee Gallup Organization, De Keulenaer works on "Flash Eurobarometer" projects, a set of 15 to 20 surveys ordered each year by the European Commission to measure the attitudes of European citizens. Some polls investigate the issue du jour, such as a survey in February that highlighted opinions on higher education reform across the European Union. Others, such as the series investigating how locals are adapting to the euro, track trends in attitudes and behavior (see graphic on p. 1060).

Public opinion polls take the social temperature on everything from government programs to citizen well-being. "Happiness is a big issue for government," says Bobby Duffy, deputy managing director of the Social Research Institute at Ipsos MORI, which employs 900 researchers. "People have quite clear ideas about what they want." Duffy's work—and De Keulenaer's—helps policymakers know what those ideas are.

The work of public opinion pollsters requires grounding in basic social science research methods, such as how to ask good questions. Most Scots will answer in the affirmative if asked whether they favor Scottish independence from the United Kingdom, notes Robert Johns, a social researcher at the University of Strathclyde in Glasgow. But when given a range of options for governance, "support for independence plummets," he says. "In a way, both are valid. It's purely a function of question design."

As if quantifying feelings weren't hard enough, cultural quirks can skew results. De Keulenaer's latest project measures life satisfaction, a topic of interest to governments everywhere and a sociological hot spot. But it's hard to compare happiness across cultures, she explains, when some countries are intrinsically happier than others—or say they are, at least. Danes claim to be very happy with their lives, as do Americans—which is odd, she continues, considering how different the countries are. De Keulenaer's training helps her navigate these national tendencies and coax insightful answers out of the sea of optimism.

An evolving field

The demand for public opinion research is growing, says Oliver Krieg, a spokesperson for TNS Emnid, a German political and social research company with 12 researchers on staff. London-based MORI grew from about 100 researchers to 400 in the 10 years before it merged with Ipsos, another public opinion research company, in 2005.

But media and governments' appetite for survey information, coupled with the advent of instant communication, hasn't just caused the industry to grow. It has also sped the pace of the work. Whereas newspapers previously asked for results in a week, they now want data within hours. And deadlines, often, are absolute. "On Election Sunday, when you have a prognosis at 6 p.m., you can't publish at 6:15," says Heiko Gothe, project manager at Infratest dimap, a Berlin company with a dozen researchers monitoring voter attitudes in Germany. "It's very usual that we have a tough time schedule."

Gothe's training is in political science, but he chose public opinion research for its "possibility to combine scientific methods in a pragmatic field." One key to the job, he says, is writing: Because media clients will quote a report verbatim, researchers must present their findings in a way the public can easily understand—while staying meticulously accurate.

Although survey design employs long-established techniques, public opinion researchers also have to keep up with new approaches. "We're constantly reacting to new survey technologies to see if they have the potential as a research tool," says De Keulenaer. Improving research methods adds another tributary in her work stream of proposing and designing surveys, then analyzing and writing up the results.

By taking a scientific approach to cultural understanding, De Keulenaer and her colleagues help politicians and policymakers keep the big picture—and the attitudes of their constituents—in view.

–KRISTA ZALA

Krista Zala is a news intern in *Science*'s U.K. office.

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Recirculating Chillers

The Neslab ThermoFlex 900 and 1400 recirculating chillers deliver up to 900 and 1400 watts, respectively, of continuous cooling capacity. The units can maintain temperatures from 5 °C to 40 °C. The chillers were designed for easy installation and operation plus high reliability and low maintenance. An integrated ramp allows a single person to unpack and install a unit, while a quick-start guide walks the user through the simple start-up process. These chillers incorporate a new, patented recirculation system with an integrated funnel, full-flow filtration, and visual fluid level indication for easy maintenance. The air and fluid filters can be changed while the unit is operating, with no need to take it off-line. Pumping capacities range up to 4.1 gpm, and adjustable pressures range to 100 psi.

Thermo Fisher Scientific For information 603-430-2211 www.thermo.com/thermoflex

Vibrating Blade Microtomes

The Leica VT1200 and VT1200 S vibrating blade microtomes for sectioning fixed or unfixed tissue specimens feature a new blade holder design that minimizes vertical deflection of the blade and protects delicate specimens, such as brain, spinal cord, and other mammalian tissues from mechanical damage. The instrument's stability and the minimized vertical deflection result in sections of high quality, with greater numbers of viable cells retained on the section surfaces. The semi-automated VT1200 is for users who prefer to manually control sectioning parameters such as section thickness and cutting stroke for each individual section. Recommended for multi-user laboratories, the VT 1200 S offers semi-automated and fully automated modes. It offers automatic feeding, specimen retraction, and a cutting window. Settings for up to eight users can be stored. Both instruments feature a newly designed blade holder that can be rotated through 90° to allow safe insertion of a whole double-edged razor, sapphire, or injector blade. The removable ice bath and buffer tray allow working under physiological conditions.

Leica For information 800-248-0123 www.leica-microsystems.com

Flow Cytometer Loader

The MPL (multi-platform loader) option for the Cell Lab Quanta SC Flow Cytometry System enables accurate, quick handling of a range of plate types, including 96-well (flat, round, or deep), 384-well, and chilled, as well as 24 ViCell sample cup holders. The MPL acts as a pipetting station, aspirating from eight sample cups on a reagent tray. Applications for the MPL option include high-throughput cell-based assays and cell viability assays in drug discovery. The Quanta SC is a personal flow cytometer for drug discovery and basic clinical research. It combines side light scatter detection and a third fluorescent channel with Coulter volume measurement to deliver accurate, multiparameter cell counting and sizing. Up to five parameters can be studied at once.

Beckman Coulter For information 714-993-8955 www.beckmancoulter.com

Humidity and Temperature Monitor

The Traceable Remote Alarm RH/Temperature Monitor features a remote temperature/humidity sensor with a seven-foot cable. It is suitable for routine measurements, round-the-clock monitoring, quality control needs, and critical experimental requirements. The sensor can be placed in hoods, clean rooms, coolers, stockrooms, incubators, environmental chambers, desiccators, and chemical storage areas. The display simultaneously shows high, low, and current humidity or temperature. A minimum and maximum memory feature for both temperature and humidity permits monitoring conditions overnight, on weekends, or any other time period. Humidity range is 20% to 99% with a resolution of 1%. Temperature range is from −50 to 70 °C. Resolution is 0.1°.

Control Company For information 281-482-1714 www.control3.com

Protein Precipitation Plate

The protein precipitation plate, p33, allows 96 samples to be handled simultaneously, using a method in which samples are treated with acetonitrile to denature the protein, which is then filtered out. The protein precipitation happens in situ in the wells. The p3 incorporates a novel treated dual-frit matrix, eliminating wetting-out and leaking of sample through the plate before the application of vacuum. The treated-frit matrix maintains high flow rates, enabling quick sample preparation times. In independent tests, the p3 plate has been shown not to have any major adverse non-specific binding problems.

Porvair Sciences For information +44 1932 240255 www.porvair-sciences.com

Thermal Analysis Tool

The Dynamic Mechanical Analyzer (DMA) 8000 thermal analysis instrument includes a number of features that enable scientists to analyze samples more easily and quickly. The DMA 8000 has a rotating analysis head that can be oriented through a full 180 degrees for ease of sample mounting and changing. It cools rapidly with minimal liquid nitrogen consumption. It also offers precise humidity and temperature control as a sample's properties are studied, along with an integrated fluid bath for immersion of a sample during testing.

PerkinElmer For information 781-663-6900 www.perkinelmer.com/dma8000

Literature

Infrared Fluorescent Products Guide details a major expansion of reagent products, including infrared-labeled secondary antibodies, protein labeling kits, protein immunoblotting kits, In-Cell Western assay kits, protein immunoblotting buffers, and protein stains. New IRDye-conjugated secondary antibodies include donkey anti-mouse, donkey anti-goat, and donkey anti-rabbit.

LI-COR Biosciences For information 402-467-0750 www.licor.com

Newly offered instrumentation, apparatus, and laboratory materials of interest to researchers in all disciplines in academic, industrial, and government organizations are featured in this space. Emphasis is given to purpose, chief characteristics, and availability of products and materials. Endorsement by *Science* or AAAS of any products or materials mentioned is not implied. Additional information may be obtained from the manufacturer or supplier.

POSITIONS OPEN

DISTINGUISHED PROFESSOR of BIOLOGY

The Division of Biology of Kansas State University (KSU) invites applications for the newly established position of **ALICE D. FIEDLER DISTINGUISHED PROFESSOR.** This individual will also be affiliated with the Terry C. Johnson Center for Basic Cancer Research. We are searching for a leader in the general area of molecular and cellular biology approaches to basic cancer research. A Ph.D., M.D., or equivalent is required. Applicants should have a record of research productivity and extramural funding consistent with the very competitive salary to be provided for this endowed professorship. Generous startup funds and laboratory space (about 3,000 square feet) will be provided. This individual is expected to catalyze further excellence in an already active program in molecular and cellular biology and basic cancer research. Further information is available at **website: http://www.ksu.edu/biology/FiedlerProfessor.** Applicants should submit a letter of interest, curriculum vitae, and description of future research plans to: **Dr. Rob Denell, Fiedler Search Committee Chair, Division of Biology, 116 Ackert Hall, Kansas State University, Manhattan, KS 66506-4901.** Nominations are also encouraged. Reference letters will be arranged for candidates under active consideration. Application screening will begin June 1, 2007, and the position is expected to be filled by June 2008. *KSU is an Equal Employment Opportunity/Affirmative Action Employer, and actively seeks diversity among its employees.*

The University of Texas at Austin, Division of Nutritional Sciences **(website: http://www.he.utexas.edu/ntr),** Department of Human Ecology, College of Natural Sciences, seeks candidates for a nine-month tenure-stream position. Applicants of any rank will be considered. The successful candidate will have, and is expected to maintain, a strong, externally funded behavioral and/or laboratory-based research program in one of the Division's focus areas (nutrition and cancer, nutrition and aging, obesity). Candidates should also have a strong record of teaching excellence at the undergraduate and graduate levels. The Registered Dietician credential is preferred but not required. Outstanding applicants may also be considered for the **DAVID BRUTON JR. CENTENNIAL PROFESSORSHIP in NUTRITIONAL SCIENCES.** Applicant instructions: This is a tenure-stream academic appointment on a nine-month basis. Review of applications will begin immediately and continue until the position is filled. A letter of application, curriculum vitae, statement of research interests, and a list of five references (who will not be contacted without the consent of the candidate) should be sent to: **Dr. Stephen Hursting, Chair, Search Committee, Division of Nutritional Sciences, 1 University Station A-2700, The University of Texas at Austin, Austin, TX 78712-0141. (E-mail: shursting@mail.utexas.edu).** All inquiries will be treated confidentially. Qualified women and minorities are encouraged to apply. Background check conducted on applicant selected. *The University of Texas at Austin is an Affirmative Action/Equal Opportunity Employer.*

The USDA, Animal and Plant Health Inspection Service, Foreign Animal Disease Diagnostic Laboratory on Plum Island, New York, is seeking a full-time **SUPERVISORY VETERINARY MEDICAL OFFICER** (GS-15; annual salary of $115,929 to $145,400 plus benefits). Incumbent will serve as the **DIRECTOR** of the facility. *The incumbent must be a U.S. citizen and able to obtain a secret security clearance while employed for the position.* A copy of announcement number 24VS-2007-0175 (open to the public) or 6VS-2007-0223 can be obtained at **website: http://jobsearch.usajobs.opm.gov,** or call **telephone: 515-663-7266** for aplication procedures. This position will be open April 30 through May 29, 2007. *The Federal Government is an Equal Employment Opportunity Employer.*

POSITIONS OPEN

PIONEER.
A DuPont Company

RESEARCH COORDINATOR

Pioneer Hi-Bred International, Incorporated, a DuPont company, is the world leader in the discovery, development, and delivery of elite crop genetics. We are looking for a Research Coordinator to provide leadership for soybean transformation in support of discovery and product development transformation. The position is located in Wilmington, Delaware. The successful candidate will lead a group responsible for providing bacterial and plant tissue culture media as well as managing growth chamber and greenhouse operations and associated plant care. This successful candidate will work with directors and other researchers to establish project goals for each of these areas and ensures that these goals are achieved. The individual will also work with others in the Transformation Department to develop strategic direction for soybean transformation programs. A Ph.D. in plant or biological science and at least six to eight years of relevant research experience beyond the Ph.D., as well as experience in plant biotechnology, preferably in the plant tissue culture/transformation areas, is necessary. Experience with soybean transformation is an advantage.

Requisition identification for this position is 5177BR. For a complete job description and to apply, go to **website: http://www.pioneer.com/careers.** *Equal Opportunity Employer.*

The University of California, San Diego (UCSD), Department of Pediatrics **(website: http://www-pediatrics.ucsd.edu)** and Children's Specialists of San Diego **(website: http://childrensspecialists.com)** are recruiting a **RESEARCH DIRECTOR** for the unified Division of Pediatric Cardiology. This is a unique opportunity to develop an exceptional research program in pediatric cardiology in San Diego, the seventh largest and most desirable city in the United States. The Basic Science Laboratories are on campus at UCSD, adjacent to many other major research institutions. The successful candidate will possess the qualifications for tenured appointment at the rank of **FULL or ASSOCIATE PROFESSOR.** Candidates must have an M.D., M.D.-Ph.D., or Ph.D. degree. This appointment will require wide recognition of research accomplishment, demonstrated leadership, and excellent teaching skill. The Division has eight pediatric cardiologists, two cardiothoracic surgeons, and an Accreditation Council for Graduate Medical Education-approved fellowship. The 220-bed clinical facility at Rady Children's Hospital serves as the only regional tertiary care hospital for children and is the major teaching facility for the Department of Pediatrics of the UCSD School of Medicine. Applications received by June 30, 2007, or until the position is filled, will receive full consideration. Salary commensurate with University of California scale. Please send curriculum vitae with four references to: **Joel Lavine, M.D., Ph.D., Search Committee Chair (e-mail: jolavine@ucsd.edu)** or by mail to: **University of California Medical Center, 200 W. Arbor Drive, San Diego, CA 92103-8450.** *UCSD is an Affirmative Action/Equal Opportunity Employer with a strong institutional commitment of excellence through diversity.*

SENIOR SCIENTIST position available to investigate applications of advanced imaging methodologies in developmental biology and neurodegenerative disease studies. Individuals with at least four years of experience in small animal model systems are encouraged to apply.

Send curriculum vitae to **Ms. K. Hilands** at **M/C 139-74, 1200 E. California Boulevard, Pasadena, CA 91125.**

University of Bergen

is a city university. Parts of the campus are in fact situated in the town centre. We have about 17.000 students and nearly 3000 employees. UiB is renowned for its research which holds a high European standard and we have three Centres of Excellence (CoE). The University of Bergen has a strong international profile which entails close co-operation with universities all over the world.

Professor in Oceanography and Director at NERSC

The Geophysical Institute has an opening for a professorship in oceanography. The successful candidate will also be offered the post as Director of the Nansen Environmental and Remote Sensing Center (NERSC).

The applicant should be an internationally recognized researcher within the areas of oceanography/climate/remote sensing. Applicants should have substantial research leadership experience as well as experience in coordinating research activities and in strategic research planning. Candidates should further demonstrate strong interpersonal skills and the ability to work and communicate well with others in a team environment. Salary is negotiable.

Procedures and criteria for application are given at http://melding.uib.no/doc/Ledige_stillinger/1177479945.html.
A description of the position is available at http://www.uib.no/mnfa/stillingsomtaler/professorat/Oceanography-Director-NERSC_07.htm

For additional information on the position please contact the Head of the Geophysical Institute, Peter M. Haugan (phone +47 55 58 26 78; email peter.haugan@gfi.uib.no) or the Chair of the NERSC Board, Dag L. Aksnes (phone +47 913 17 497; email dag.aksnes@bio.uib.no).

Applications should be addressed to Geophysical Institute, The University of Bergen, Allég. 70, NO-5007 Bergen, Norway. Please do not send applications by e-mail.

Closing date for applications: 1 June 2007. Quote reference No: 07/3091/MN.

NERSC

CICERO ab

PENNSTATE

Milton S. Hershey Medical Center
College of Medicine

ORTHOPAEDIC BIOENGINEERING FACULTY POSITION AVAILABLE

The Pennsylvania State University, Division of Musculoskeletal Sciences, Department of Orthopaedics and Rehabilitation at Penn State College of Medicine announces a search for an Assistant or Associate Professor (tenured or tenure track) in the area of orthopaedic bio or mechanical engineering. This position includes a highly competitive salary and significant start-up funds. The successful candidate will be an individual who can apply engineering concepts to the study of musculoskeletal tissues. This is a unique opportunity to join a well-established, highly interactive research group consisting of engineers, material, clinical and basic scientists focusing on musculoskeletal research. Additional bioengineering faculty with interests in medical devices, biomaterials, imaging and drug delivery may be found in the Biomedical Engineering Institute within the College of Medicine and in the Department of Bioengineering within the College of Engineering. A joint academic appointment will include a primary appointment in the College of Medicine and a secondary appointment in an appropriate department of the College of Engineering at Penn State.

The Department of Orthopaedics and Rehabilitation is expanding its research base which will become an integral component of a newly established Institute of Musculoskeletal Disease. The successful candidate will establish close collaborations with a newly established Nano and Regenerative Medicine Institute. The Penn State College of Medicine is located in Hershey, Pennsylvania and offers a highly desirable lifestyle and an affordable cost of living in close proximity to many metropolitan areas including Baltimore, Washington, D.C., Philadelphia and New York City. Applications will be accepted until the position is filled.

Send curriculum vitae to:

Ananya Das, Engineering Search Committee
Division of Musculoskeletal Sciences
Department of Orthopaedics and Rehabilitation
The Pennsylvania State University College of Medicine
500 University Drive, H089, Hershey, PA 17033

For your health, Hershey Medical Center is a smoke-free campus. Penn State is committed to affirmative action, equal opportunity and the diversity of its workforce. The ad was approved by Penn State University.

FIU

FLORIDA INTERNATIONAL UNIVERSITY
Miami's public research university

OPEN POSITIONS COLLEGE OF MEDICINE

Florida International University (FIU) will open a new College of Medicine- the first medical school to open in a major metropolitan area in a quarter –century and the first public medical school in south Florida.

During the next two years the College's founding faculty will develop an innovative, twenty-first century curriculum, and begin construction of new research and instructional facilities. Special areas of interest include Reproduction and Development as well as Environmental Sciences and Toxicology. Faculty are solicited to fulfill roles in educational leadership in:

Clinical Medicine
Professional Development of Physicians
Cellular and Molecular Biology
Human and Molecular Genetics
Physiology
Pharmacology
Human Anatomy, Embryology and Development

Candidates should have a doctoral degree, a minimum of 5 years experience in medical education and experience in medical education leadership.

Interested applicants may apply online at **www.fiujobs.org**, position #6004, e-mail a CV and list of 3 professional references to **medjobs@fiu.edu** or mail a CV and list of 3 professional references to: **Joe Leigh Simpson, M.D., Executive Associate Dean for Academic Affairs, Florida International University, College of Medicine, 11200 SW 8th Street, HLS 693, Miami, Florida 33199.**

Candidates will continue to be considered until all positions are filled.

FIU is a member of the State University System of Florida and is an Equal Opportunity, Equal Access Affirmative Action Employer.

NIDDK

Tenure-Track Position in Human Energy Metabolism
National Institute of Diabetes and Digestive and Kidney Diseases

We seek an outstanding scientist to direct a vigorous, innovative research program in human energy metabolism and serve as Director of the newly established Metabolic Core Laboratory (MCL), Clinical Endocrinology Branch, NIDDK. The MCL performs a number of analyses including exercise testing, physical activity monitoring, body composition measurement, and 24-hour energy expenditure analysis in health and disease. Applicants must be highly motivated and have a demonstrated track record through publications that address significant contributions in the areas of energy expenditure and physical activity as it relates to metabolism and weight regulation. The successful candidate is expected to develop an independent, world-class research program complementary to current investigations within the Branch and to successfully oversee the functioning of the MCL. The position comes with generous start up funds and on-going support.

The Clinical Endocrinology Branch, NIDDK is located on the main NIH campus in Bethesda, Maryland, a suburb of Washington DC. The Branch represents interests similar in range to those of an academic department. There are strong interactions among the independent research groups, and the position offers unparalleled opportunities for interdisciplinary collaboration within NIDDK and throughout NIH. Applicants should submit a curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and arrange for three letters of reference to be sent to:

Dr. James Balow, Chair, Search Committee, c/o Glynnis Vance, NIDDK, 9000 Rockville Pike, Building 10-CRC/Room 5-2551, National Institutes of Health, Bethesda, MD 20892.

Application Deadline: **June 8, 2007**

NIDDK

Tenure-Track Position in Endocrinology and Metabolism and Human Obesity
National Institute of Diabetes and Digestive and Kidney Diseases

We seek an outstanding scientist to direct a vigorous, innovative research program in the Clinical Endocrine Section of the Clinical Endocrinology Branch to advance knowledge in the area of obesity and weight regulation with particular emphasis on the neuroendocrine aspects of weight regulation and the role of sleep in obesity. Applicants must be highly motivated and have a demonstrated track record through publications that address significant contributions to the field of endocrinology and metabolism. The successful candidate is expected to develop an independent, world-class research program complementary to current investigations within the Branch. The position comes with generous start up funds and on-going support.

The Clinical Endocrinology Branch, NIDDK is located on the main NIH campus in Bethesda, Maryland, a suburb of Washington DC. The Branch represents interests similar in range to those of an academic department. There are strong interactions among the independent research groups, and the position offers unparalleled opportunities for interdisciplinary collaboration within NIDDK and throughout NIH. Applicants should submit a curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and arrange for three letters of reference to be sent to:

Dr. James Balow, Chair, Search Committee, c/o Glynnis Vance, NIDDK, 9000 Rockville Pike, Building 10-CRC/Room 5-2551, National Institutes of Health, Bethesda, MD 20892.

Application Deadline: **June 8, 2007**

WWW.NIH.GOV

NIDDK Tenure-Track Position in Clinical Research in Diabetes and Kidney Disease
National Institute of Diabetes and Digestive and Kidney Diseases

We seek an outstanding scientist to direct a vigorous, innovative clinical research program in the epidemiology, physiology, and treatment of type 2 diabetes, diabetic nephropathy, and related disorders. Applicants must be highly motivated and have a demonstrated track record through publications that address significant issues of causation, prevention, and treatment of these conditions. Applicants must also be licensed to practice medicine in one of the United States and have substantial experience in community relations, recruitment, and clinical research among US minority groups. The successful candidate is expected to develop an independent, world-class research program complementary to current investigations within the Phoenix Epidemiology and Clinical Research Branch (PECRB). The position comes with generous start up funds and on-going support.

The PECRB, NIDDK is located in Phoenix, Arizona. The Branch represents interests similar in range to those of an academic department. There are strong interactions among the independent research groups, and the position offers unparalleled opportunities for interdisciplinary collaboration within NIDDK and throughout NIH. Applicants should submit a curriculum vitae, bibliography, copies of three major publications, a summary of research accomplishments, a brief statement of future research goals, and arrange for three letters of reference to be sent to:

Dr. James Balow, Chair, Search Committee, c/o Glynnis Vance, NIDDK, 9000 Rockville Pike, Bldg. 10-CRC/Rm. 5-2551, National Institutes of Health, Bethesda, MD 20892.

Application Deadline: **June 8, 2007**.

NIDDK POSTDOCTORAL FELLOWSHIPS IN MOLECULAR AND CELL BIOLOGY
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

We are seeking outstanding postdoctoral candidates holding a PhD, an MD or an MD-PhD with a background in molecular and cell biology and genetics interested in the following research topics:

A) IDENTIFICATION OF NOVEL REGULATORS OF MESENCHYMAL STEM CELL SPECIFICATION

The laboratory studies the transcriptional regulation of adipogenesis and is currently interested in the characterization of novel molecules that can influence adipocyte cell lineage specification. If you would like to apply for a postdoctoral position in this laboratory, please send your curriculum vitae with a cover letter to Dr. Elisabetta Mueller (elisabettam@niddk.nih.gov). To learn more about our research, please visit our lab website at **http://intramural.niddk.nih.gov/research/faculty.asp?People_ID=1702**

B) SKELETAL MUSCLE STEM CELL REGULATION

Our laboratory studies the role of TGF-beta family members in skeletal muscle development and metabolism. A postdoctoral position is available to study the regulation of adult skeletal muscle stem cell quiescence and activation. Please send your curriculum vitae with a cover letter to Dr. Alexandra McPherron (mcpherrona@niddk.nih.gov). To learn more about our research, please visit our lab website at **http://intramural.niddk.nih.gov/research/faculty.asp?People_ID=1701**

C) BIOLOGY OF SPHINGOLIPID SIGNALING

The laboratory studies the signaling functions of sphingolipids, a diverse group of cellular lipids, with focus on their roles in immunity and inflammation. If you would like to apply for a postdoctoral position in this laboratory, please send your curriculum vitae with a cover letter to Dr. Richard Proia (proia@nih.gov). To learn more about our research, please visit our lab website at **http://intramural.niddk.nih.gov/research/faculty.asp?People_ID=1533**

Applications will be reviewed upon receipt. The selected candidates will be contacted for an interview within a month from the application.

ETH

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Assistant Professor for Heterogeneous Catalysis

ETH Zurich invites applications for a faculty position on the assistant professor level in Heterogeneous Catalysis. The successful candidate will be expected to build upon the strengths of the Department while adding a new aspect to the field. Research will focus on a significant area of heterogeneous catalysis. Active participation is expected in teaching the curriculum of chemical and bioengineering.
Candidates should provide evidence of international recognition of their research achievements in catalysis. The ability to cooperate with both academic and industrial colleagues is essential. Courses at Master level may be taught in English.

Assistant professorships have been established to promote the careers of younger scientists. The initial appointment is for four years with the possibility of renewal for an additional two-year period.

Please submit your application together with a curriculum vitae and a list of publications to the **President of ETH Zurich, Raemistrasse 101, CH-8092 Zurich, no later than July 15, 2007.** With a view toward increasing the number of female professors, ETH Zurich specifically encourages female candidates to apply.

FACULTY POSITION

The Department of Anatomy and Cell Biology at Downstate Medical Center invites applications for a tenure-track faculty position.

The successful candidate is expected to have an independent, extramurally-funded research program in the cardiovascular sciences and to participate in teaching medical students and graduate education.

Preference will be given to candidates with prior teaching experience and training in stem cell research. Curriculum vitae, a brief description of previous and anticipated research, and the names of three references should be sent to:

Dr. M.A.Q. Siddiqui
Professor and Chair
Department of Anatomy & Cell Biology
State University of New York
Downstate Medical Center
450 Clarkson Avenue, Box 5
Brooklyn, NY 11203

FAX: 718-270-3732
E-mail: MAQ.Siddiqui@Downstate.edu

SUNY DOWNSTATE Medical Center

SUNY Downstate is an EOE

香 港 大 學
THE UNIVERSITY OF HONG KONG

Founded in 1911, The University of Hong Kong is committed to the highest international standards of excellence in teaching and research, and has been at the international forefront of academic scholarship for many years. Of a number of recent indicators of the University's performance, one is its ranking at 33 among the top 200 universities in the world by the UK's Times Higher Education Supplement. The University has a comprehensive range of study programmes and research disciplines, with 20,000 undergraduate and postgraduate students from 50 countries, and a complement of 1,200 academic members of staff, many of whom are internationally renowned.

Director of Safety
(Ref.: RF-2006/2007-522)

Applications are invited for the appointment as Director of Safety in the Safety Office from July 1, 2007 or as soon as possible thereafter. The appointment will initially be made on a three-year fixed-term basis, with the possibility of renewal.

Applicants should possess a university degree, preferably a postgraduate qualification, plus 15 or more years of appropriate experience, of which at least 5 years should be at managerial level, together with a qualification from a professional safety and health institute.

The appointee will head the Safety Office and reports to the Vice-Chancellor, via a Pro-Vice-Chancellor. The major role of the appointee is to advise and make recommendations to the University on matters of environmental health and safety and to implement the University safety policy. For further details of the post, please refer to the website at https://www.hku.hk/apptunit/.

A highly competitive salary commensurate with qualifications and experience will be offered. The appointment will attract a contract-end gratuity and University contribution to a retirement benefits scheme, totalling up to 15% of basic salary. The appointment carries leave, and medical/dental benefits. Housing benefits will be provided as applicable.

Further particulars and application forms can be obtained at https://www.hku.hk/apptunit/, or from the Appointments Unit, The University of Hong Kong (Fax: (852) 2540 6735; E-mail: senrappt@hkucc.hku.hk). **Closes June 4, 2007. Candidates who are not contacted within 6 months of the closing date may consider their applications unsuccessful.**

The University is an equal opportunity employer

UNIVERSITY OF MISSOURI-COLUMBIA

Assistant/Associate Professor of Medicine

Full time position for a physician scientist who is board eligible/certified in rheumatology as Assistant/Associate Professor of Medicine is available in the Division of Immunology and Rheumatology, Department of Internal Medicine, University of Missouri-Columbia. This position will be tenure track. Primary responsibility will be to develop an independent research program. Generous start up package, laboratory space, and protected time will be provided (limited care responsibilities will be expected at this time). Collaborative opportunities exist for basic and clinical research in a variety of fields, including molecular biology, human cellular immunology and animal models of autoimmunity.

Address inquiries to **Dr. Robert Ortmann, Department of Internal Medicine, UMC, MA438 Medical Science Building, Columbia, MO 65212. IMFaculty@health.missouri.edu.**

UMC is an equal opportunity affirmative action employer and complies with the ADA act of 1990: Women and minorities are encouraged to apply. Questions and ADA accommodation needs may be addressed to Jessica Hosey, (573) 884-2825.

Visit the University of Missouri-Columbia's web site at http://mujobs.missouri.edu

BASF Conference on Nanomaterials

BASF
The Chemical Company

OCTOBER 21 – 23, 2007 IN SINGAPORE

Nanotechnology is considered to be one of the most important emerging technologies worldwide. Through the controlled manufacture and structuring of materials, it allows the creation of completely new product properties. It is an innovation driver for many industry sectors. BASF is one of the leading companies in the field of chemical nanotechnology.

The BASF conference on Nanomaterials will foster the exchange of ideas, techniques, experiments and applications. A series of lectures will be given in order to match BASF's future vision with current activities of the research institutes in the field of Nanomaterials. Leading scientists from all over the world will be participating in the conference as speakers on the following topics:

1. Nanomodified and nanostructured materials and foams
2. Synthesis and modification of nanoparticles
3. Nanotechnology for electronics
4. Interface of bio- and nanotechnology

Invitation procedure

The conference is open to every young researcher at the PhD, post-doctoral or junior professor level, working in the four fields mentioned above. Full scholarships for participation are available – please send your CV and an abstract for a poster referring to these topics to andreas.a.fechtenkoetter@basf.com by June 30, 2007.

We look forward to meeting you in Singapore.

www.basf.com

Albany Medical College

Faculty Positions
Center for Cardiovascular Sciences

Albany Medical College invites applications for tenure-track faculty positions at all ranks in the Center for Cardiovascular Sciences. We seek highly motivated individuals with a record of research productivity to participate in an interactive group engaged in cellular, molecular, and genetic cardiovascular research and graduate education. We are particularly interested in applicants who have translational interests in cardiac/vascular pathophysiology in order to complement existing strengths in vascular cell signaling, smooth muscle reactivity, endothelial barrier function, and nitric oxide biology. A Ph.D. or M.D./Ph.D. degree and three years of productive post-doctoral experience are minimal requirements for appointment at the Assistant Professor level. Applicants for Associate or Full Professor should have appropriate experience and a nationally recognized and funded research program.

Investigators in the Center for Cardiovascular Sciences have opportunities for collaboration with scientists at neighboring institutions, including the Bioengineering Dept. at Rensselaer Polytechnic Institute, SUNY Albany College of Nanosciences and Center for Functional Genomics, the Ordway Research Institute and the New York State Wadsworth Laboratories. The area offers diverse cultural and recreational attractions with easy access to Boston, New York City, and the Adirondack, Catskill, and Berkshire Mountains. For further information about the Center and Albany Medical College, please visit **www.amc.edu**.

Applicants should submit a current curriculum vitae, description of research interests, and three letters of recommendation by **August 1, 2007** to:

Dr. Harold A. Singer
Chair, CCS Search Committee
Director, Center for Cardiovascular Sciences
Albany Medical College (MC-8)
47 New Scotland Ave.
Albany, New York 12208

An Equal Opportunity/Affirmative Action Employer.
Women and Minorities are encouraged to apply.

Dream. Challenge. Succeed.

BIOCHEMISTRY FACULTY POSITION

The Department of Molecular and Cellular Biochemistry invites applications for a tenure track faculty position at the Assistant, Associate, or Full Professor level. Successful candidates must possess a Ph.D., M.D. or equivalent degree. Individuals at the Associate, or Full Professor level are expected to have a proven track record of independent research and sustained extramural funding. We are seeking individuals to complement existing departmental programs including, but not limited to the areas of diabetes, cardiovascular disease, neuroscience, and cancer research, but we welcome all qualified applicants.

The successful candidate will benefit from a stimulating and collaborative environment within the department and a strong graduate program. Competitive start-up funds, salaries, state-of-the-art facilities and appropriate space will be offered in a new 185,000 ft² research building.

Evaluation of applicants will begin July 2007. Please email your application materials, a curriculum vitae and a description of your current and future research program. Candidates should also submit three references via email or mail to:

MCB Faculty Search Committee
Email: lapres0@uky.edu
B278 Biomed. Biol. Sc. Res. Bldg.
741 South Limestone St.
Lexington, KY 40536-0509

UK
UNIVERSITY OF KENTUCKY

For further information about the Department, visit: **www.mc.uky.edu/biochemistry**

The University of Kentucky is an equal opportunity employer and encourages applications from minorities and women.

DIRECTOR FOR RESEARCH

Edinburg Regional Academic Health Center Campus of the University of Texas Health Science Center at San Antonio

The University of Texas Health Science Center at San Antonio (UTHSCSA) and the Regional Academic Health Center (RAHC) Campus invite applications from candidates at the Associate or Full Professor level interested in leading an innovative basic and translational science research program at our new 60,000 square foot research facility in Edinburg, Texas, which features a vivarium and a certified Bio-safety Level 3 facility. This position provides a unique opportunity for health disparities research in diseases that disproportionately affect Hispanics and border populations. Edinburg is located in the Lower Rio Grande Valley, the fastest growing region in Texas. Qualifications are an M.D. or PhD, proven ability to conduct outstanding scholarly work, obtain peer-reviewed funding and serve as a Principal Investigator on multi- and inter-disciplinary research teams. Broad administrative experience, in depth knowledge of funding systems in health-related research and excellent communication skills are also essential. Responsibilities include developing and leading a multidisciplinary program working on problems of particular importance to South Texas, for example, diabetes, obesity, infectious diseases and cancer. The Director will also be expected to maintain his or her own research and mentor junior investigators. This position reports directly to the RAHC Regional Dean and will involve close coordination with the Associate Dean for Research of the UTHSCSA School of Medicine.

Applicants interested in applying should submit a letter describing interests and CV to: **Robin L. Brey, M.D., Associate Dean for Research, University of Texas Health Science Center at San Antonio, School of Medicine, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900; Email: brey@uthscsa.edu**. Review of applications will start immediately and continue until the position is filled.

More information about the Edinburg RAHC Research Facility can be found on our website at **www.rahc.uthscsa.edu**.

The University of Texas Health Science Center at San Antonio is an Equal Employment Opportunity/Affirmative Action Employer.
All faculty appointments are designated as security sensitive positions.

FACULTY POSITION

Assistant/Associate/Full Professor

The Department of Pharmaceutical Sciences at Texas Tech University Health Sciences Center (TTUHSC) seeks applicants for two tenure-track faculty positions in Pharmacology or drug-related fields at the **Assistant/Associate/Full Professor** level.

The Department presently has 20 full-time faculty and >38 graduate assistantships with research interests in drug design, drug delivery, receptor signaling, and biotechnology/immunotherapeutics. Critical focus areas of the campus and Department include Cancer Biology, Cardiovascular & Stroke, Neurobiology, and Women's Health. The Department is supported by >20,000 sq ft of research and animal space as well as an array of critical common equipment including confocal microscope, LC-MS/MS, flow cytometer, and FTIR. In 2006, the Department was ranked 6th in the nation in percent of pharmacy faculty with NIH funding. The Department will be expanding over the next four years with 7 new faculty slots and a new biomedical/pharmaceutical research building immediately adjacent to the School of Pharmacy and School of Medicine in Amarillo. For further details on our Department, please visit our website: http://www.ttuhsc.edu/sop/PharmSci/.

Applicants must have an earned doctorate with relevant postdoctoral experience. In addition to maintaining an extramurally funded research program, the successful candidate will teach in the basic science components of the Pharm.D and Ph.D. curriculum, and mentor graduate students.

Competitive start-up packages, incentive package and lab space are available. Applicants should submit documents online by July 6, 2007 at http://jobs.texastech.edu (**Job Requisition # 61359**). Please include a curriculum vitae, a summary of research and teaching interests and names and addresses of three references. For questions, contact the search committee chair, **Dr. Margaret Weis, Texas Tech University School of Pharmacy, 1300 Coulter, Amarillo, TX 79106;** Email: margaret.weis@ttuhsc.edu; Fax: 806-356-4034.

TTUHSC is an Equal Opportunity/Affirmative Action Institution.
Minorities and Women are encouraged to apply.

Associate Dean for Research
College of Dental Medicine

MUSC
MEDICAL UNIVERSITY OF SOUTH CAROLINA

The Medical University of South Carolina (MUSC) invites nominations and applications for the position of Associate Dean for Research, College of Dental Medicine (CDM). The Associate Dean for Research reports to the Dean of the College of Dental Medicine and is responsible for visionary leadership and administration of the college's research mission.

Notable accomplishments of the CDM research program in the past five years include a comprehensive NIDCR T32 Institutional Training grant in 2006 (including funding for the DMD/PhD program, postdoctoral fellows, and short-term dental student research projects: **DMSTP.musc.edu**), a NIDCR U24 infrastructure development grant in 2004 (**ORALHEALTH.musc.edu/research_program/index.htm**), and the NCRR funded South Carolina COBRE (Center of Biomedical Research Excellence) in Oral Health in 2002 (**ORALCOBRE.musc.edu**).

Growth in the CDM's research capacity is a reflection of major expansion in MUSC's research mission as well as the CDM's strategic importance in the institutional research portfolio. As part of its growing research enterprise, the college houses the Center for Oral Health Research (**ORALHEALTH.musc.edu**) and has significant programs with the state Bioengineering Alliance. Thus, we are seeking an established, dynamic scientist to build upon this foundation for the next phase of program growth.

The CDM is one of six colleges at the MUSC, a publicly supported, freestanding academic health sciences center located in the beautiful, historic city of Charleston. Nationally known for its strong clinical training, the CDM has recently entered a phase of targeted development in oral health research. The college recently broke ground for a new state of the art clinical educational facility, which will include a clinical research unit.

Applicants must possess an earned doctoral degree. Individuals holding both the DMD/DDS and PhD degrees are preferred. The successful candidate will have academic credentials appropriate for appointment as a full professor, including a distinguished record of scholarly productivity, extramural funding, administrative leadership, and teaching. Successful candidates will have experience in dental education, excellent interpersonal communication skills, and a demonstrated ability to attract financial support for the college and its research programs. A commitment to the college's continued leadership in oral health research across MUSC is required.

Review of applications will begin immediately and continue until **August 30, 2007**. All applications will be submitted electronically at **http://www.musc.edu/hrm/careers/executive.htm** and should include a letter of application with qualifications, current curriculum vitae, and a list of five references.

For more information or nominations contact **Ms. Anne Hantske, Office of the Dean, CDM MUSC at (843) 792-3811**.

MUSC is an EEO/AA Employer.

PENNSTATE
University Park

Director

The Pennsylvania State University seeks applications and nominations for an innovative Director of the Penn State Institutes of Energy and the Environment (PSIEE). The PSIEE was established in 1999 to develop and integrate new knowledge of the biological and physical environment and its impact on individual and social well-being. In the past year, an energy science and engineering component was coupled with the PSIEE's environmental mission. We seek to continue to improve our understanding of the relationships between human society, energy and the environment, and develop innovative approaches to achieving societal goals for the sustainable use of energy and the environment. The objectives of PSIEE are: to increase the visibility of Penn State's energy and environmental research and education programs; to facilitate the ability of faculty and students to address opportunities that require interdisciplinary interaction and collaboration; and to engender new research and education directions. State-of-the-art instrumentation is available across the full spectrum of energy and environmental sciences and engineering, ranging from capabilities to probe biological, biochemical, and biogeochemical processes and properties at the fundamental molecular level to computational facilities for simulating basic biophysical processes, human consequences of environmental change and energy use, or for simulating changes in the earth system. In conjunction with the Huck Institutes of the Life Sciences and the Materials Research Institute at Penn State, opportunities exist for utilizing an animal transgenic facility and core facility in high throughput DNA sequencing and proteomics, structural biology and computational science, mass spectrometry and electron microscopy. As a part of this initiative, the University has hired 8 senior faculty and 20 junior faculty in key disciplines of the PSIEE in a University-wide effort to increase the visibilities and stature of an already strong, diverse program of environmental research and education.

The University has just announced the funding of 24 new faculty positions in areas of energy-related research to support this new initiative of the PSIEE; awarding of these positions will be guided by the new director.

The Director of PSIEE reports directly to the Senior Vice President for Research, who oversees a research activity exceeding $657 million annually. The responsibilities of the Director include: (1) administering the core multidisciplinary research facility with research contracts of approximately $42 million in active contracts; (2) proactively fostering collaboration among the core colleges and developing policies and faculty incentives for active faculty participation, which builds an atmosphere of inclusion of diverse perspectives; (3) chairing the faculty coordinating council, which oversees all PSIEE activities and provides leadership, direction, and vision; (4) identifying faculty opportunities and coordinating research programs; (5) coordinating undergraduate and graduate programs in environmental and energy studies across colleges; and (6) serving as liaison between the University's energy and environmental programs and state, national, and international energy and environmental organizations. The Director will contribute to and promote existing strengths of Penn State in the areas of air quality, biodiversity and ecosystems, global change, health and the environment, industrial ecology and green engineering, and water resources. Priority areas for energy include, efficient fossil energy use, bioenergy systems, hydrogen energy production storage and fuel cells, the nuclear fuel cycle and solar energy.

Candidates must have a Ph.D. or equivalent degree in one of the energy/environmental science or engineering disciplines and must have credentials appropriate for a tenured professor in an appropriate college. The successful candidate will be recognized as an international leader in energy/environmental sciences in terms of scientific accomplishments and vision; possess leadership skills necessary to advance ongoing and new initiatives in research, teaching and outreach in environmental sciences and engineering; and have an appreciation for the academic environment and our land grant mission.

Review of applications will begin on May 14, 2007 and will continue until the position is filled.

Nominations may be sent as follows:
Robert Santoro, Chair
PSIEE Search Committee
The Pennsylvania State University
304 Old Main
University Park, PA 16802
jep5@psu.edu

Penn State is committed to affirmative action, equal opportunity and the diversity of its workforce.

PENN STATE ***Making Life Better***

Max-Planck-Gesellschaft
Max Planck Society

Selbstständige Nachwuchsgruppen

(Independent Junior Research Groups)

The Max Planck Society invites applications from outstanding young scientists in the field of **Biology and Medicine**.

Successful applicants will have demonstrated the ability to perform excellent research. They will be offered an

Independent Junior Research Group Leader position

(W2; equivalent to associate professor level without tenure) including a five-year grant (research positions, budget, investments) at one of the following Max Planck Institutes:

MPI for Medical Research, Heidelberg

MPI for Biophysical Chemistry, Göttingen

MPI of Immunobiology, Freiburg

Applications should include a CV, a list of publications, copies of three publications, a one-page summary of scientific achievements, and a two-page research plan. For further information and detailed application instructions see

http://www.snwg.mpg.de

The Max Planck Society is committed to equal opportunities and to employing disabled persons.

The deadline for application is **June 11, 2007.**

CHAIR
Department of Biochemistry

Duke University School of Medicine announces a search for an outstanding scientist and leader to Chair the Department of Biochemistry. The Department of Biochemistry has strong programs in biological membranes, DNA replication and repair, transcription and RNA biochemistry, enzyme mechanisms and cofactors, free-radical biochemistry, physical biochemistry, computational protein design, and structural biology and bioinformatics. Six primary faculty are members of the National Academy of Sciences, and the Department has well-established doctoral and postdoctoral training programs. Significant resources are available to the Chair for recruiting new and established faculty. Opportunities are available for strong interactions with the Institute of Biological Structure and Design, the Institute of Genome Science and Policy, as well as other departments and centers at Duke.

The Chair shall be a recognized leader in the field of Biochemistry and will hold the rank of full Professor or equivalent. The Chair must display a strong commitment to the mentoring of faculty, students and fellows, demonstrate a vision for the development of strong programs in emerging research areas, foster interactions with university-wide initiatives and programs, and promote the integration of departmental research and educational programs within those of the Medical Center and University. In addition to a distinguished record of scholarship, the ideal candidate would have academic administrative experience and a commitment to work collaboratively within an academic medical center and university.

Applicants should submit their curriculum vitae, a statement addressing research interests and academic leadership goals, and the names and contact information of three references to: **Biochemistry Chair Search Committee, c/o Ms. Kathleen Barbee, Duke University School of Medicine, Box 2927, Durham NC 27710. Email: biochemsearch@mc.duke.edu, Phone: (919) 668-6502 and Fax: (919) 684-0208**. Consideration of applications will begin immediately and will continue until the position is filled.

Duke University Medical Center is an Equal Opportunity/Affirmative Action Employer. Women and underrepresented minorities are encouraged to apply.

FACULTY POSITION
Assistant/Associate/Full Professor in Pharmaceutics

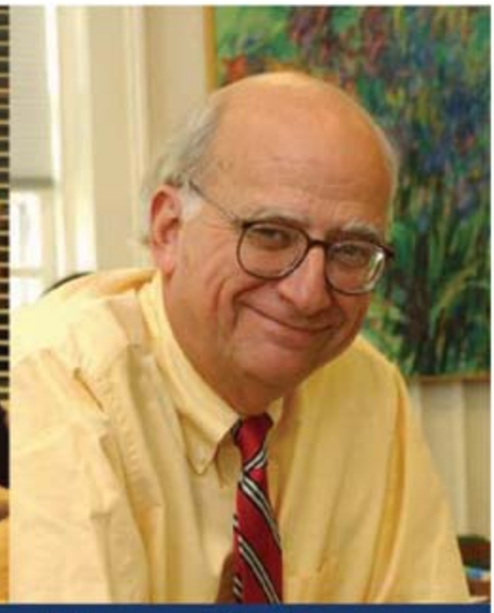
The Department of Pharmaceutical Sciences at Texas Tech University Health Sciences Center (TTUHSC) seeks applicants for two tenure-track faculty position in Pharmaceutics/Drug Delivery at the **Assistant/Associate/Full Professor** level.

The Department presently has 20 full-time faculty and >38 graduate assistantships with research interests in drug design, drug delivery, receptor signaling, and biotechnology/immunotherapeutics. The Department is supported by >20,000 sq ft of research and animal space as well as an array of critical common equipment including confocal microscope, LC-MS/MS, flow cytometer, and FTIR. The University supports separate research centers on Cancer Biology, Cardiovascular & Stroke, and Women's Health. In 2006, the Department was ranked 6th in the nation in percent of faculty with NIH funding. The Department will be expanding over the next four years with 7 new faculty slots and a new biomedical/pharmaceutical research building immediately adjacent to the School of Pharmacy. TTUHSC at Amarillo includes the School of Pharmacy, School of Medicine and the Harrington Cancer Research Center. For further details, please visit our website: http://www.ttuhsc.edu/sop/PharmSci/.

Applicants must have an earned doctorate with relevant postdoctoral experience in Pharmaceutics, Pharmacokinetics or Drug Delivery. In addition to maintaining an extramurally funded research program, the successful candidate will teach in Pharm.D and Ph.D. programs and mentor graduate students.

Competitive start-up packages and lab space are available. Applicants should submit documents online to http://jobs.texastech.edu (**Job Requisition # 61762**). Please include a curriculum vitae, a summary of research and teaching interests and names and addresses of three references. For questions, contact the search committee chair, **Dr. Fakhrul Ahsan, Texas Tech University School of Pharmacy, 1300 Coulter, Amarillo, TX 79106;** Email: fakhrul.ahsan@ttuhsc.edu. Fax: 806-356-4034.

TTUHSC is an Equal Opportunity/Affirmative Action Institution. Minorities and Women are encouraged to apply.



MAHZARIN R. BANAJI
Harvard University

ELIZABETH F. LOFTUS
University of California, Irvine

MICHAEL S. GAZZANIGA
University of California, Santa Barbara

The Faces and Minds of Psychological Science

Discovering Unconscious Bias

MAHZARIN R. BANAJI was one of the first scientists to develop the idea of unconscious forms of bias – the ability to make judgments of people, using knowledge of their social group, without awareness. Banaji's research has influenced numerous disciplines including law, public policy, medicine, education, and business. Most recently, she has been conducting groundbreaking research on the origins of prejudice in young children, the origins of social cognition (using neuroimaging), and the flexibility of humans to adapt to new situational demands.

Revolutionizing the Role of Eyewitness Testimony

ELIZABETH F. LOFTUS's research on false memories and eyewitness testimony has made her one of the most influential psychologists in the U.S. legal system today. By demonstrating experimentally how memory is vulnerable to suggestion, bias, and other influences, she has exposed the fallibility of eyewitness testimony in the courtroom. Her findings have also revolutionized police methods for interrogating witnesses, and changed how defendants are prosecuted.

An "Interpreter" of the Brain

A pioneer in neuroscience, MICHAEL S. GAZZANIGA's research uncovered the separate functioning of the left and right hemispheres of the brain. He has continued to define the frontiers of cognitive psychology throughout his career, and most recently has explored the "interpreter" system in the brain. This mechanism guides our actions, emotions, and responses to our environment, and may hold the key to understanding consciousness. He is also a leader in national science policy and, as a member of the President's Council on Bioethics, has advocated strongly for increased stem cell research.

These distinguished researchers are leaders in the exciting field of psychological science. Using the latest methods and technologies, they have made enormous strides in exploring the complexities of human behavior in all of its forms, from the most basic brain research to applications in health, education, business, and social issues.

Psychological science covers the full spectrum of behavior, from the fundamental brain processes involved in how we think, learn, and remember, to the way that people function in groups and organizations, and everything in between. What unites these diverse efforts is a commitment to scientific rigor and to the advancement of the public well-being through science-based understanding of the human condition.

We Mind Science

For insights from psychological science into our mysterious and often quirky human nature, read the weblog "We're Only Human . . ." at www.psychologicalscience.org/onlyhuman.

aps
ASSOCIATION FOR PSYCHOLOGICAL SCIENCE
www.psychologicalscience.org

VCU Massey Cancer Center
Virginia Commonwealth University

SENIOR FACULTY POSITION IN CHEMICAL BIOLOGY

Faculty Position #F1961

The Massey Cancer Center, the NCI-designated Cancer Center of Central Virginia, has committed substantial resources in Chemical Biology to interdigitate with its current programs in cancer cell signaling, cancer genetics and epigenetics, molecular cancer therapeutics, immunology, radiation biology and oncology, and cancer prevention and control. We are currently seeking a senior faculty member in any area of chemical biology, including chemical genetics or any use of small molecules as probes of biological function aimed at understanding and/or therapeutically approaching the functions gained and lost during the initiation and progression of human cancers. Collaborative interactions with investigators in structural biology, computational chemistry, mass spectrometry and proteomics, and mouse genetics would be available. The position is tenure track and would involve a faculty appointment in the academic department of Virginia Commonwealth University appropriate for the individual candidate. The position will be supported in part by an endowed chair and significant additional resources through the Cancer Center. We are seeking an innovative and interactive colleague, with a history of leadership and major grant funding. Laboratory space will be provided in the new 80,000 sq ft Massey Cancer Center Goodwin Research Laboratory on the Medical College of Virginia campus of VCU. Candidates should have a Ph.D. and/or M.D. degrees, proven excellence, originality and productivity in research and a strong interest in graduate and professional teaching.

Virginia Commonwealth University is ranked internationally and nationally as a top research institution. With more than 30,000 students, VCU is the largest public, urban, doctoral-granting university in Virginia. The university offers more than 195 certificate, undergraduate, graduate, professional and doctoral programs in 15 schools and one college. Massey Cancer Center, a growing NCI-designated cancer center, is VCU's focal point for basic and clinical cancer research, education and cancer health delivery. Its 175 member researchers have appointments in 25 academic departments.

Application Process: Please submit an application letter, curriculum vitae, a statement of citizenship or visa status, and the names of three individuals to be contacted as references to: **Chemical Biology Search, c/o Personnel Administrator; Virginia Commonwealth University Massey Cancer Center; P.O. Box 980037; Richmond, VA 23298-0037.** The position will remain open until filled.

Virginia Commonwealth University is an Equal Opportunity/Affirmative Action Employer. Women, minorities, and persons with disabilities are encouraged to apply.

Preliminary announcement for a Professorship in Research of New Target Molecules and Gene Therapy

The University of Kuopio (UKU) is an internationally respected research-intensive university. The University is profiled in health, environment and well-being, and the research focus areas cover especially molecular medicine, drug research and biotechnology. A. I. Virtanen Institute for Molecular Sciences (AIVI) at UKU forms the core of Biocenter Kuopio, and houses altogether 11 research groups. AIVI's research activities are concentrated on molecular medicine of major diseases of high importance for health care (cardiovascular diseases, neurodegenerative diseases, metabolism-related diseases) with the strong expertise in molecular and cellular mechanisms of the diseases, disease modelling, prevention and therapy of the diseases (gene and cell-based therapy, pharmaceutical intervention), and *in vitro* and *in vivo* imaging. AIVI houses two Centers of Excellence in Research, one national and one Nordic. Please find more at **http://www.uku.fi/aivi/**.

AIVI announces a new Professorship in the field of Research of New Target Molecules and Gene Therapy. Candidates with proven track records in any subfield of molecular medicine or molecular pharmacology will be taken into consideration. Ability to conduct high quality externally funded research in collaboration with other groups of AIVI and UKU, especially with those of the Faculty of Pharmacy (http://www.uku.fi/farmasia/english/), is considered essential for the post-holder.

Interested candidates are encouraged to submit their expression of interest by **15th of June, 2007** by e-mail to Riitta Keinänen, Head of the Institute Administration (riitta.keinanen@uku.fi) with the following attached documents: **1.** Curriculum Vitae, four (4) pages max. **2.** List of all publications. **3.** Publications (max 20) which the candidate considers as the most relevant in regard to the field of the Professorship. **4.** Research plan, four (4) pages max. **5.** Description of proposed activities in research collaboration, networks and funding, two (2) pages max

The salary of the professor will depend on the qualifications of the applicant according to the salary system of the Finnish universities. The position will initially be filled, either by invitation or application, for a period of five (5) years.

For more information, contact: Jari Koistinaho, Dean of the A. I. Virtanen Institute for Molecular Sciences (jari.koistinaho@uku.fi) tel. +358 17 162 427.

UNIVERSITY OF KUOPIO

TRINITY COLLEGE DUBLIN

The University of Dublin

www.tcd.ie/vacancies

Trinity College is recognised internationally as Ireland's premier university and is the only Irish university to rank in the top 100 world universities (78th) and amongst the top 50 European universities (25th). We are recruiting world class leaders in research and education to advance our research strengths, develop our fourth level graduate education and build on our excellence in third level undergraduate education. Our strategic priorities of research and education are also aligned with contributing to the national goal of fostering Ireland's cultural and economic vibrancy.

School of Biochemistry and Immunology

Chair of Biochemistry (1960)

(re-advertised)

The School of Biochemistry and Immunology at Trinity College Dublin invites applications for the Chair of Biochemistry (1960) tenable from 1 September 2007 or as soon as possible thereafter.

The School seeks an individual who will provide innovative and energetic leadership and has a strong commitment to academic excellence at a major research university. The successful candidate will be an internationally recognised scholar in any area of biochemistry and an academic leader of the highest calibre with a proven track record of research and teaching.

The appointee will join a dynamic team of researchers whose interests span all areas of biochemistry. The research interests of the candidate will be expected to complement those currently in the School of Biochemistry and Immunology and to support the School's undergraduate and postgraduate teaching programmes.

The successful candidate will be expected to take a leadership role in the School and will serve a term as Head of School and/or Head of the Discipline of Biochemistry in due course, in accordance with College regulations.

Information about the research interests of the School of Biochemistry and Immunology can be found at http://www.biochemistry.tcd.ie/. Further particulars of the appointment, including the application procedure and details of salary may be obtained from:

Michael Gleeson, Secretary to the College, West Theatre, Trinity College, Dublin 2

Telephone: +353-1-896-1722. Fax: +353-1-671-0037. Email: moya.thompson@tcd.ie

to whom formal applications may be sent to arrive by the preferred closing date of noon on Friday 29 June 2007.

Trinity College is an equal opportunities employer

Karolinska Institutet

PROFESSOR IN GENOME INTEGRITY

Karolinska Institutet invites applications for a postion as professor in Genome Integrity.

For further details please contact Professor Anna Wedell, Dept of Molecular Medicine and Surgery, Karolinska University Hospital, Solns, phone +46 8 517 765 35, email: **Anna.Wedell@ki.se** or the SACO union representative Professor Tomas Olsson, Dept of Clinical neuroscience, Karolinska University Hospital, Solna, phone +46 8 517 762 42, email: **Tomas.Olsson@ki.se**

Please state your qualifications in accordance with the Karolinska Institute qualification portfolio available on the Web page **http://info.ki.se**

Deadline for application is June 25, 2007. Reference no 152/ 07-221, Registrar, Karolinska Institutet, SE-171 77 Stockholm, Sweden.

For the entire advertisement please look at **http://jobb.ki.se/internal/general/starteng.asp**

E-mail: **Registrator@ki.se**

AWARDS

Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences

Hamdan Award for Medical Research Excellence

In the field of:

THERAPY IN MALIGNANCY

▪

MOLECULAR THERAPY IN DRUG TARGETING (PHARMACOGENOMICS)

▪

ORGAN & TISSUE TRANSPLANTATION

The prize amount is AED three hundred thousand (AED 300,000) (Approx. US$ 82,000) **to be awarded equally to 3 winners.**

The general secretariat is pleased to invite doctors, researchers, universities, research centres and medical scientific societies throughout the world to submit their research work for the awards 2007-2008

Closing Date: November 30, 2007

For further information :

The General Secretariat
Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences
P O Box 22252, Dubai, United Arab Emirates
Tel: +971 4 3986777
Fax: +971 4 3984579 / 3980999
E mail: shhaward@emirates.net.ae
Website: http://www.hmaward.org.ae

GRADUATE PROGRAM

BIOZENTRUM Universität Basel

UNI BASEL

OPPORTUNITIES FOR EXCELLENCE

International PhD program at the BIOZENTRUM of the University of Basel, Switzerland

The **Biozentrum** together with the **Werner Siemens-Foundation (WSF)**, Zug (Switzerland) launches the **International PhD program** in **Molecular Life Sciences** and encourages excellent students to apply for one of the prestigious WSF fellowships.

The Biozentrum provides an internationally renowned research environment centered around three focal areas (Infection Biology, Growth and Development, Neurobiology) and two core programs (Structural Biology & Biophysics and Genome Scale Biology & Bioinformatics) and is dedicated to basic molecular and biomedical research (http://www.biozentrum.unibas.ch/). We offer advanced, interdisciplinary training in the field of modern biology, a lively and interactive educational atmosphere, and competitive salaries with respect to European standards. University graduates admitted to the Program receive theoretical and practical training, and conduct a three-year research project under the supervision of a Biozentrum faculty member, monitored by a Thesis Advisory Committee.

Applications to the program have to be submitted online. Application forms, requirements, and additional information can be found under: http://www.biozentrum.unibas.ch/phd/.
Application deadline: July 1st, 2007.

POSITIONS OPEN

RESEARCH ASSISTANT PROFESSOR
in Radiation Biology
International Institute of Nano and Molecular Medicine
University of Missouri-Columbia
Department of Radiology

The University of Missouri-Columbia International Institute of Nano and Molecular Medicine (I2NM2) seeks to fill a full-time position in radiation biology at the rank of Research Assistant Professor for spring 2007. Salary is commensurate with experience.

Qualifications: earned Doctorate in radiation biology or related discipline; substantial research experience in biological experiments pertaining to neutron capture therapy (NCT) including tumor induction,

NCT agent assessment and tissue analysis; supervisorial experience in neutron irradiation of animals; extensive experience in fluorescence and confocal microscopy; ability to develop a research program and procure extramural funding; and willingness to mentor postdoctoral, graduate, and undergraduate students.

The successful candidate is expected to develop an outstanding, externally funded research program and participate in teaching. Position qualifications include a Ph.D and a record of promising, creative research in nanomedicine. Submit curriculum vitae, a description of current and projected research, and three letters of reference to: **Director (M. Frederick Hawthorne, Ph.D.), Position Search, International Institute of Nano and Molecular Medicine, University of Missouri-Columbia, 202 Schlundt Hall, Columbia, MO 65212.** Electronic documents should be sent to **e-mail: hawthornem@health.missouri.edu.** *The University of Missouri is an Equal Opportunity/Affirmative Action Employer. To request ADA accommodations, please contact our* ***ADA Coordinator*** *at* ***telephone: 573-884-7278 (Voice/TTY).***

ASSISTANT PROFESSOR of ENTOMOLOGY, Montana State University, twelve-month tenure-track appointment. Candidates must have a Ph.D. in entomology or related field. Complete position announcement and application procedure may be seen at **website: http://www.montana.edu/level2/jobs.html.** Screening begins August 1, 2007, start date approximately January 1, 2008. *ADA/Equal Opportunity/Affirmative Action/Veterans' Preference Employer.*

POSITIONS OPEN

UNIVERSITY OF SOUTH CAROLINA

TENURE-TRACK FACULTY POSITIONS AVAILABLE

The University of South Carolina (USC) is undergoing rapid and unprecedented growth. Applications are invited for several tenure-track **ASSISTANT/ASSOCIATE/FULL PROFESSOR** positions in the areas of cancer, immunology, cell and molecular biology, signaling, biodefense/medical microbiology, and AIDS. Research experience related to existing faculty strengths in the areas of cancer, immunology, medical microbiology, toxicology, drugs of abuse, complementary and alternative medicine, and eye diseases will be preferred. Candidates for the Assistant Professor position must have a Ph.D. or M.D. or D.V.M./V.M.D. or equivalent with postdoctoral research experience. Candidates for Associate/Full Professor positions should have current extramural funding. Competitive salary, attractive startup funds, and excellent core facilities are available. Candidates are expected to develop a strong, extramurally funded research program and participate in the teaching mission of the Department. The Columbia area offers a warm climate and an outstanding quality of life. Apply with curriculum vitae, statement of research plans, and three letters of recommendation to: **Dr. Mitzi Nagarkatti, Chair, Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29208** or **e-mail: pmiads@gw.med.sc.edu.** The search will start immediately and continue till positions are filled. *USC Columbia is an Equal Opportunity, Affirmative Action Employer and encourages applications from women and minorities.*

FACULTY POSITION AVAILABLE

The Barbara Ann Karmanos Cancer Institute at Wayne State University seeks an individual to conduct cancer-related research in the area of bone biology. Candidate should use novel approaches and technologies as well as animal models to determine molecular and cellular mechanisms involved in bone remodeling. Candidates must have commitment to cancer research and an ability to work with others in a multidisciplinary setting in order to drive novel approaches linking the laboratory to clinical trials with areas of interest including bone stem cell biology, signaling pathways in bone formation and turnover, and bone microenvironment. Successful candidates must be highly motivated with the ability to secure external grant funding and promote an environment of collegiality and collaboration with the Institute's and University's existing basic and clinical scientists. Rank and salary are commensurate with experience and prior accomplishments.

Applicants should have a Ph.D. and a proven track record of productivity in cancer research in the area of bone biology as well as successful completion of postdoctoral training.

All positions offer a unique opportunity to lead and develop research programs with substantial opportunity for growth. Applicants should submit a letter of interest, curriculum vitae, and three references to:

Stephen Ethier, Ph.D.
Associate Center Director for Basic Research
Deputy Director, Barbara Ann Karmanos Cancer Institute
Professor, Barbara Ann Karmanos Cancer Institute
4100 John R., Detroit, MI 48201
Fax: 313-576-8626
E-mail : ethier@karmanos.org

POSITIONS OPEN

DEPARTMENT HEAD
Department of Microbiology, Immunology and Pathology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University

The College of Veterinary Medicine and Biomedical Sciences invites applications and nominations for the position of Head of the Department of Microbiology, Immunology and Pathology **(website: http://www.cvmbs.colostate.edu).** The Department is committed to excellence in undergraduate, graduate, and professional veterinary medical education and advising, and has a strong reputation for innovation in instructional technology. The Department is internationally recognized for its research and service programs and activities; for example the faculty are major contributors to the Colorado State University (CSU) Program of Research and Scholarly Excellence in Infectious Diseases, the Rocky Mountain Regional Center for Excellence for Biodefense and Emerging Infectious Diseases, the newly formed Supercluster in Infectious Disease, and large multidisciplinary research programs that investigate arthropod-borne, mycobacterial, and prion based infectious diseases. Departmental faculty also are recognized leaders in veterinary pathology and diagnostics and provide these services through the CSU Veterinary Diagnostic Laboratory. The new Department Head will provide leadership, management, and mentorship as the Department builds on existing strengths and identifies new areas of opportunity for growth.

Applicants must have a D.V.M., M.D. or equivalent degree, and/or a Ph.D.; demonstrated excellence in scholarly activity and research; experience in and a commitment to teaching and mentoring students; and must meet requirements for appointment as a **FULL PROFESSOR.** Administrative experience is desirable. Women and minority candidates are encouraged to apply. A letter of application, curriculum vitae, and list of three references who may be contacted when appropriate, should be sent electronically to the **Chair of the Search Committee:**

Dr. Terry M. Nett
Office of the Dean
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523-1601
E-mail: terry.nett@colostate.edu

Review of applications will begin 20 September 2007, and continue until a suitable candidate is identified.

Colorado State University is an Equal Employment Opportunity/Affirmative Action Employer.

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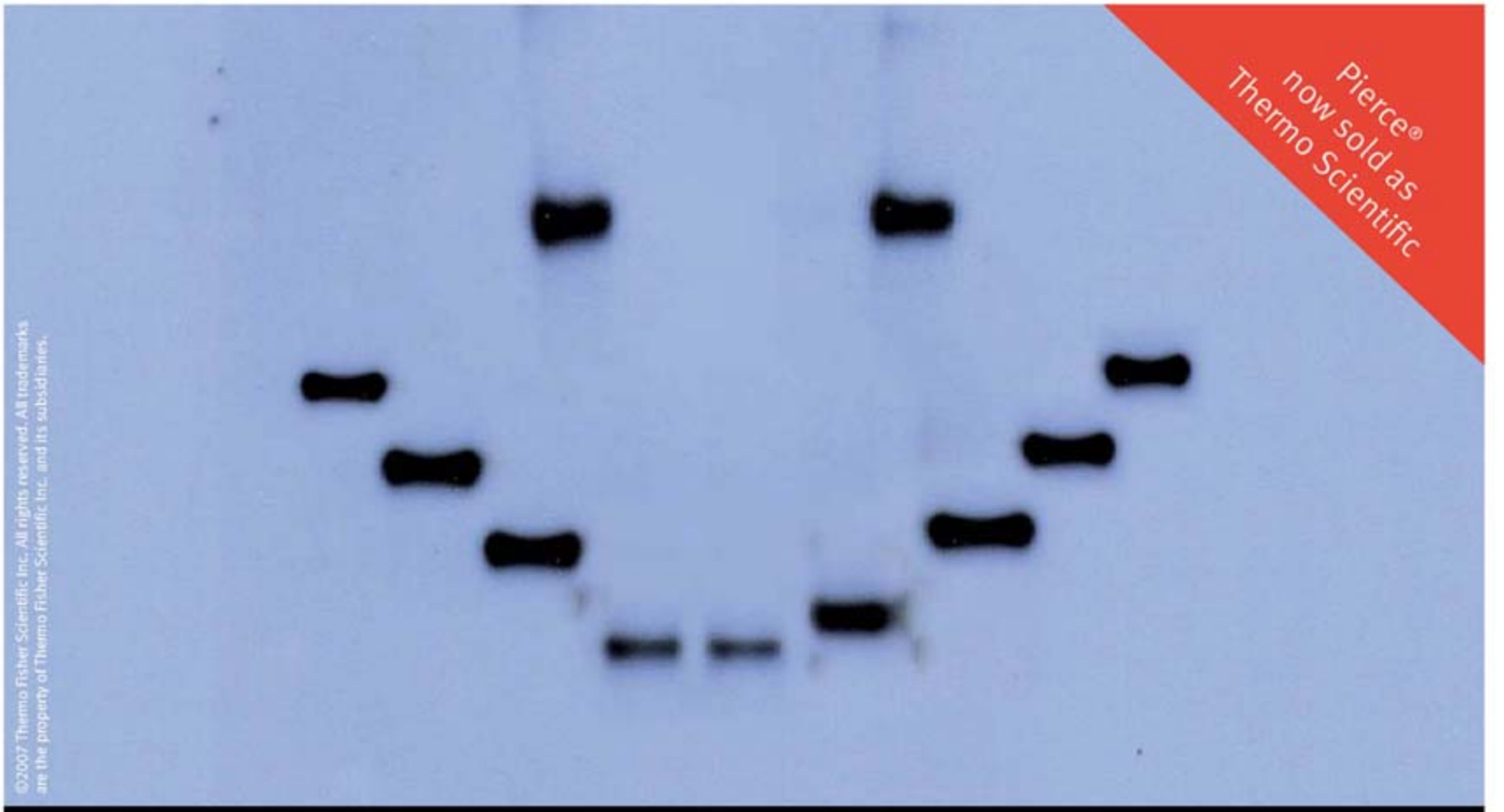

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